STUDIES ON PYRIMIDINESULPHONIC ACIDS AND RELATED COMPOUNDS: SYNTHESES AND METATHESES

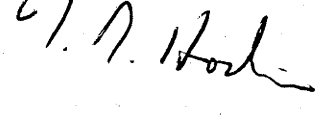
a thesis
submitted to the
Australian National University
for the degree of
Doctor of Philosophy
by

John Anthony Hoskins

Department of Medical Chemistry
John Curtin School of Medical Research
Australian National University

May 1972

The work described in this thesis was carried out by the candidate at the Australian National University. Where the work of others was employed or quoted appropriate references have been included.



ACKNOWLEDGEMENTS

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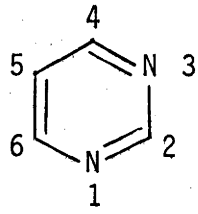
My especial thanks go to Mrs S. Schenk for her kindness and co-operation in the typing of this thesis.

I am grateful to the Australian National University for the award of a generous research scholarship.

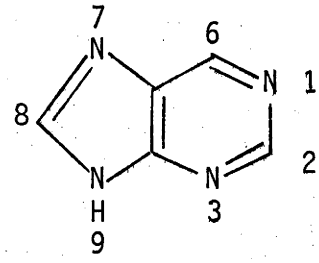
NOMENCLATURE

IUPAC nomenclature as defined in the handbook of The Chemical Society is used; in general, substituents are written in alphabetical order as prefixes to the parent name.

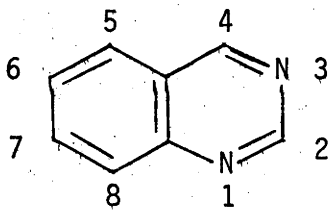
The structure and numbering of the ring systems described in this thesis are as follows:-



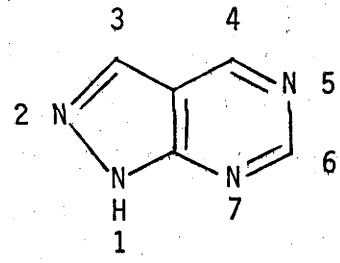
pyrimidine



purine

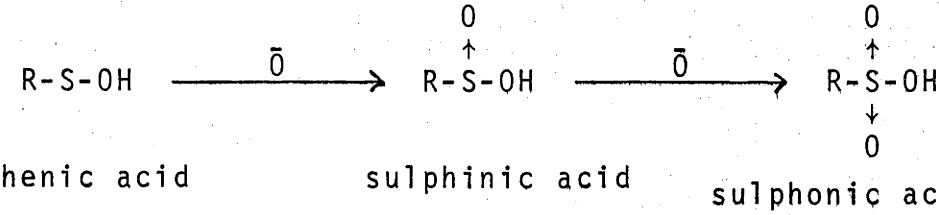


quinazoline



pyrazolo[3,4-*d*]pyrimidine

The compounds of sulphur, other than thiones, are divided into those related to sulphenic, sulphinic and sulphonic acids in which the valence number of the sulphur is formally increased from 2 to 4 to 6.



sulphenic acid sulphinic acid sulphonic acid

SUMMARY

Potassium pyrimidine-2(and 4)-sulphonates and a number of their *C*-methylated derivatives, together with some potassium purine- and quinazoline-sulphonates, have been prepared. The preparations were accomplished either by the reaction of the corresponding chloro compounds with boiling aqueous potassium sulphite solution, or by the oxidation of the corresponding thiones (thiols) with neutral aqueous potassium permanganate. The sulphonates were colourless stable compounds which generally decomposed at high temperatures without melting. A number of disulphides, possible intermediates in the above oxidation, were also prepared.

Neutral aqueous solutions of the sulphonates were stable but hydrolysis to the corresponding oxo compounds occurred readily in both acidic and alkaline solutions. The rates of these hydrolyses have been measured; for the faster hydrolyses a stopped-flow rapid-reaction technique was necessary. A similar technique was also employed for the determination of the dissociation constants of the compounds. At pH 14.0 (40^{o}) the $t_{\frac{1}{2}}$ values varied from 12 to 830 minutes and at H_{o} -1 (25^{o}) from 2 to 28 minutes, according to the position of the sulphonate group and the number and position of the methyl groups (which retard hydrolysis). The deactivating effect of a methyl group could be considerable: a 5-methyl group in a pyrimidine-sulphonate decreased the rate by up to a factor of 20.

Chlorine oxidation of a number of pyrimidinethiones in aqueous methanol saturated with potassium hydrogen difluoride (below 0^{o}) gave the corresponding sulphonyl fluorides. These compounds are colourless, low-melting, and stable when pure. Quinazoline-2-sulphonyl fluoride and the known purine-6-sulphonyl fluoride were prepared similarly.

Treatment of the sulphonyl fluorides with nitrogen-containing nucleophiles (*e.g.* hydrazine or simple amines) under mild conditions gave substituted sulphonamides through scission of the S-F bond. Under more vigorous conditions, the whole fluorosulphonyl group was displaced by the nucleophile. However, in reactions with the oxygen-containing nucleophiles, water and methoxide ion, only the latter reaction was observed and the corresponding oxo or methoxy compounds were obtained.

The rates of the reaction of the pyrimidinesulphonyl fluorides with sodium methoxide in methanol were measured. The overall rates of reaction were faster than those observed for alkaline hydrolysis of the corresponding sulphonates but the effect on the rate of each added methyl group was broadly similar.

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CHAPTER I

GENERAL INTRODUCTION

A) Introduction

This thesis deals with the synthesis, properties, and reactions of some pyrimidines and fused pyrimidines bearing a sulphur-containing group *ortho* to a ring nitrogen atom. Such *ortho* positions are naturally electron-deficient by virtue of the powerful electron-withdrawing effect of the ring nitrogens (D.J. Brown, 1962, p.6). In contrast, the 5-position of pyrimidine and the β-positions of pyridine are less electron-deficient and are described as 'aromatic', implying that the reactivity at these positions approaches that in benzene. This distinction between the two types of position is important because the electronic nature of the ring influences the properties of the sulphur-containing substituent according to the point of attachment.

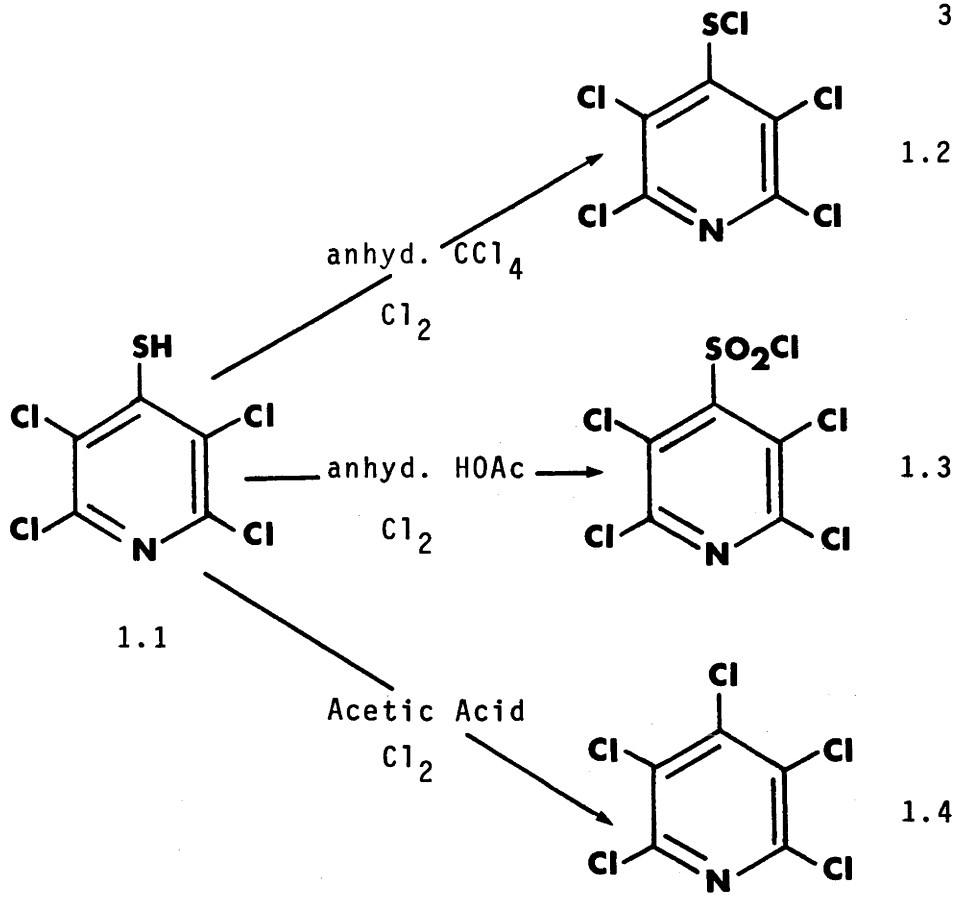
Much work has appeared on aromatic carbocyclic compounds with sulphur-containing substituents; rather less work on analogous aromatic heterocyclic compounds in which the sulphur-containing group is stabilised by occupying either the 5(β)-position or a normally-activated position but in the presence of electron-releasing substituents (which restore some measure of aromaticity to such positions); and very little work on the rather unstable simple pyrimidine-2(or 4)-sulphonic acids and related compounds. Thus any discussion of previous work must embrace systems not studied in the present work so that the new results may be seen in context.

B) Sulphenic acids and related compounds

The stability of the inorganic and organic acids of sulphur decreases as the proportion of oxygen is lowered (Reid, 1958). Frequently the salts of such acids are stable whereas the free acids are not. Anthraquinone-1-sulphenic acid is one of the very few free sulphenic acids ever described.

Sulphenic acid halides (R-SX) are well known in carbocyclic chemistry but are almost unknown in the heterocyclic field. When tetrachloropyridine-4-thiol (1.1) was oxidised at room temperature by chlorine in anhydrous carbon tetrachloride the 4-sulphenyl chloride (1.2) was formed; a similar oxidation in anhydrous acetic acid gave the 4-sulphonyl chloride (1.3); and in the presence of water, the C-S bond was broken to give pentachloropyridine (1.4) (Ager *et al.*, 1970).

Amides derived from sulphenic acids (sulphenamides; $R\text{-}SNH_2$) are more common: for example pyrimidine-2-sulphenamide (1.5; R=H) and its 4-methyl isomer (1.5;$R=CH_3$) have been prepared (Hurley and Robinson, 1965). Since their preparation *via* sulphenyl halides was precluded, such compounds were made by the chloroamination of thiols under very mild conditions; more vigorous conditions led to the formation of disulphides (Sisler *et al.*, 1970), possibly by nucleophilic attack of thiol anion on the sulphenamide first formed (Fontana *et al.*, 1966; Heimer and Field, 1970). The oxidation of sulphenamides, by



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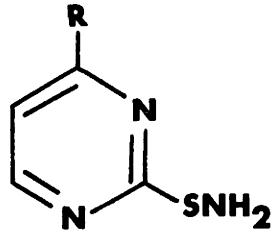

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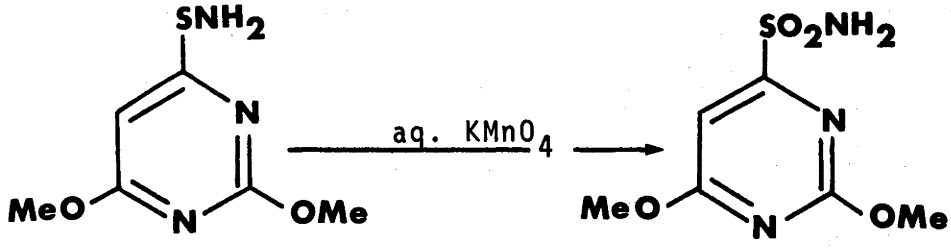

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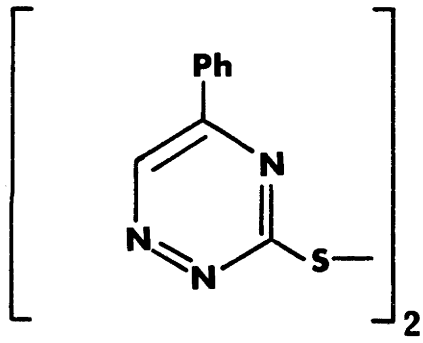
neutral aqueous potassium permanganate, to give the corresponding sulphonamides is of some importance: in the early days of sulphonamide therapy, many *N*-substituted benzenesulphenamides were so oxidised (see the patents of Bann *et al.*, 1943 and 1944; and Barber, 1943). However one of the few examples in heterocyclic chemistry is provided by the work of Greenbaum (1954) who oxidised 2,4-dimethoxy-6-sulphenamidopyrimidine (1.6) to the sulphonamide (1.7).

Heterocyclic disulphides form an important class of compounds in chemistry and biology. They are generally prepared by the oxidation of a thiol (or thione) under mild conditions. Iodine in aqueous potassium iodide has been used to prepare di(5-phenyl-*as*-triazin-3-yl) disulphide (1.8)(Tišler, 1960), di(4-methylpyrimidin-6-yl) disulphide (1.9)(Gabriel and Colman, 1899a) and di(purin-6-yl) disulphide (1.10)(Doerr *et al.*, 1961). Frequently dilute hydrogen peroxide brings about oxidation only to the disulphide stage, as in the preparation of di(2,4-dimethoxypyrimidin-6-yl) disulphide (1.11) (Greenbaum and Holmes, 1954). Nitrous acid, or isoamyl nitrite are less common reagents for the oxidation of thiols to disulphides but they have been used by Israel *et al.*(1964) for the preparation of di(4-aminopyrimidin-6-yl) disulphide (1.12). When Comrie and Stenlake (1958) oxidised pyridine-4-thiol with nitric acid a disulphide was obtained as its dinitrate salt in addition to



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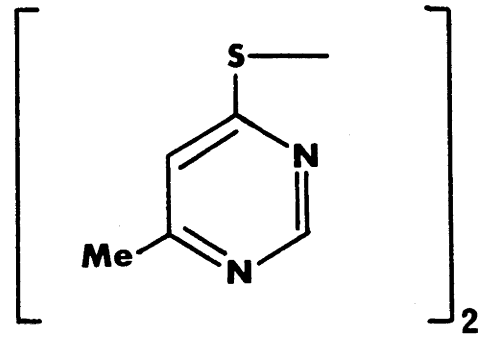

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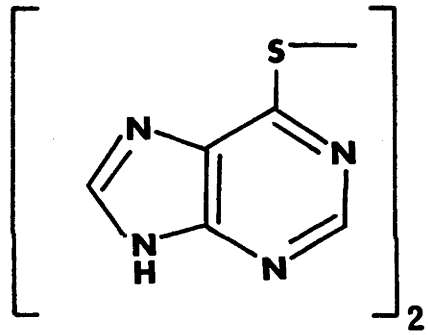

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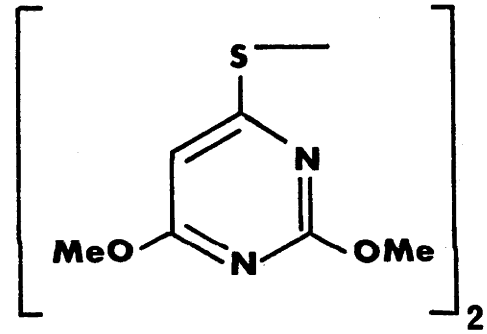

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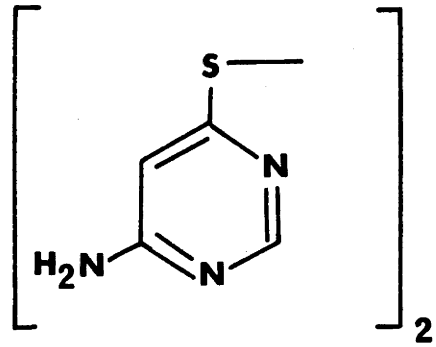

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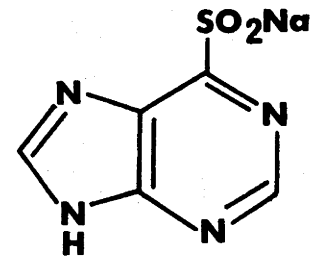

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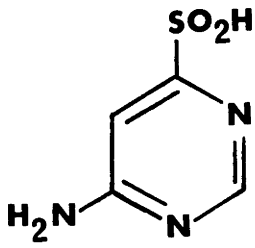
pyridine-4-sulphonic acid. In the presence of acid, thiones are oxidised to disulphides by dimethylsulphoxide or tetramethylenesulphoxide. This reaction is of special importance to n.m.r. spectroscopists since some heterocyclic thiones are isolated as their acid salts and d_6-DMSO is a common spectroscopic solvent (Wallace and Mahan, 1964; Bigum, 1972).

$$2\ RSH + (CD_3)_2SO \longrightarrow R_2S_2 + (CD_3)_2S + H_2O.$$

C) Sulphinic acids and related compounds

Very few heterocyclic sulphinic acids, or their salts, are known and none was encountered in the present work.

Sulphinic acids are well known to result from the alkaline decomposition of disulphides under oxidising conditions (Schöbel and Wagner, 1955; Schiller and Otto, 1876; Fromm, 1908); Doerr *et al.*(1961) prepared sodium purine-6-sulphinate (1.13) by this method. They bubbled oxygen through an alkaline suspension of di(purin-6-yl) disulphide (1.8) for 24 h to obtain a high yield of the sulphinate, which they described as unstable. The few known pyrimidinesulphinic acids contain electron-releasing groups, usually amino: 4-amino-6-sulphinopyrimidine (1.14) has been prepared by the oxidation (30% hydrogen peroxide) of the corresponding thione in ice-cold alkaline solution (Israel *et al.*, 1964); 4,6-diamino- (1.15) and 4,5,6-triamino-2-sulphinopyrimidines (1.16) were prepared similarly (Evans *et al.*, 1956).



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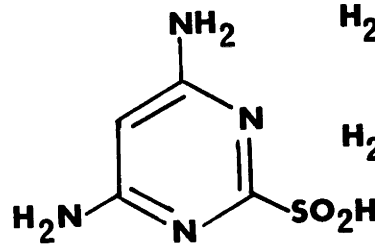

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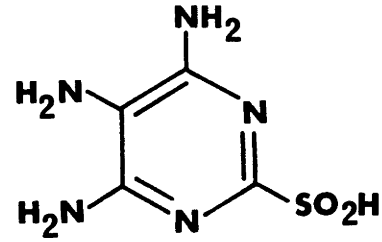

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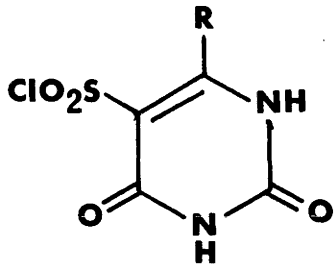

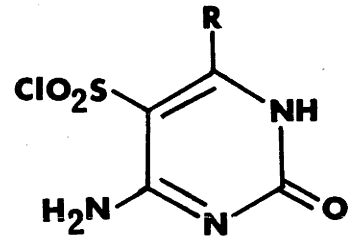

R = H or CH_3

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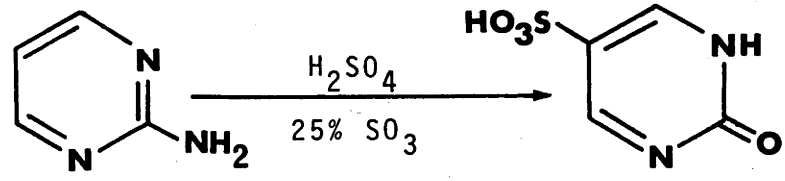

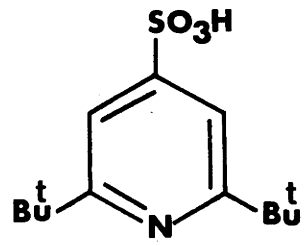

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D) Sulphonic acids and related compounds

The preparation of sulphonic acids by direct sulphonation is of very limited application in heterocyclic chemistry, particularly in electron-deficient systems. Being an electrophilic reaction sulphonation will only take place at positions of sufficiently high electron-density. Thus quinazolines are sulphonated directly only in the benzene ring (Armarego, 1967) and pyrimidines only at the 5-position (Cerfontain, 1968). Uracil (Herr *et al.*, 1956) and 6-methyluracil (Elderfield and Prasad, 1961) react with chlorosulphonic acid to give the 5-sulphonyl chlorides (1.17). 6-Methyluracil-5-sulphonyl chloride has been hydrolysed with ice-water to give the free acid (Elderfield and Prasad, 1961). In contrast, Khromov-Borisov and Karlinskaya (1954) found that cytosine and 6-methylcytosine gave directly the free sulphonic acids (1.18) on chloro-sulphonation; Caldwell and Jaffé (1959) found that 2-aminopyrimidine was sulphonated directly in oleum (25% SO_3) but the product was hydrolysed immediately to 5-sulphopyrimidin-2-one (1.19).

Because compounds used for direct sulphonation are also strong acids with oxidising and dehydrating properties they may have a profound effect on substituents (McElvain and Goese, 1943). A further complication may arise because the ring nitrogen atoms are susceptible to electrophilic attack. This is demonstrated by the

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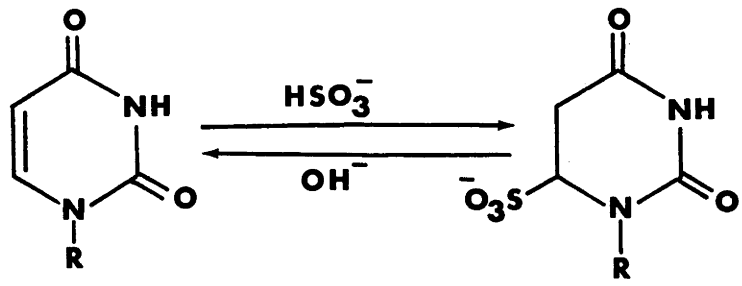

R = Sugar or H

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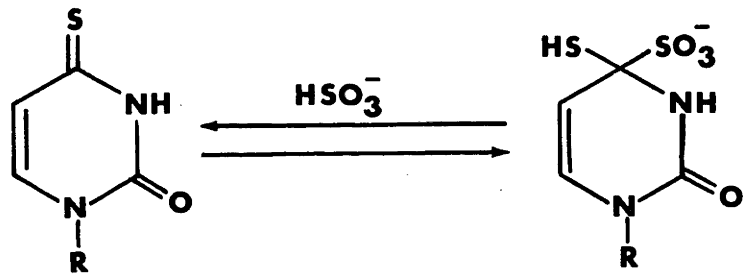
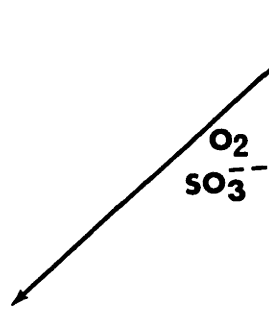
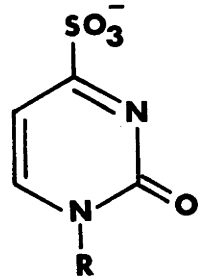


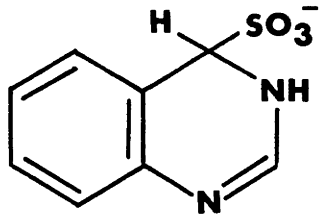
R = β-D-ribofuranosyl





reaction of six membered N-heteroaromatic compounds with sulphur trioxide at room temperature to give $\underline{N}$-SO_3 addition compounds (Kretzschmann and Fuerst, 1963). In particularly difficult cases, sulphonation at the ring carbon atoms can be effected only at high temperatures and/or in the presence of mercury as a catalyst (Cerfontain, 1968). As an interesting example of sulphonation under mild conditions, H.C. Brown and Kanner (1953) found that 2,6-di-t-butylpyridine, in which the alkyl groups presumably sterically inhibited the formation of a pyridinium complex, reacted with sulphur trioxide in liquid sulphur dioxide at -10^{o} to give a sulphonic acid, presumed by the authors to be the 4-sulphonic acid (1.20).

A sulpho group may be introduced directly into a heterocyclic ring under relatively mild conditions by an addition rather than a substitution reaction. Those *N*-heteroaromatic systems which contain at least one highly polarised double bond covalently add sodium bisulphite across this bond. This reversible reaction has been observed, for example, in the 2-methyl-1-pyridinium ion and related systems (Pitman *et al.*, 1970; Perrin and Pitman, 1965). Uracil, cytosine, and derived nucleosides behave similarly by adding bisulphite across the 5,6-double bond (1.21) (Shapiro *et al.*, 1970; Hayatsu *et al.*, 1970). A rather different reaction occurs between 4-thiouridine and bisulphite ion: here the initial adduct is converted (in the presence of oxygen and sulphite ion) into the 4-sulphonate (1.22) (Hayatsu, 1969).



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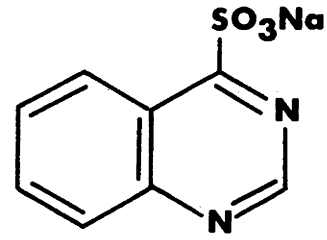

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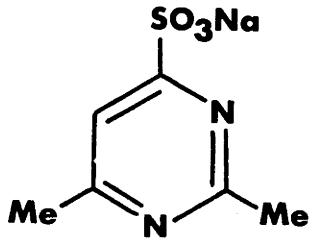

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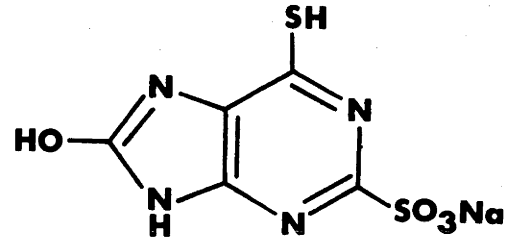
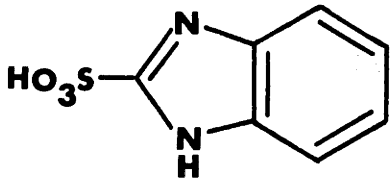


1.26



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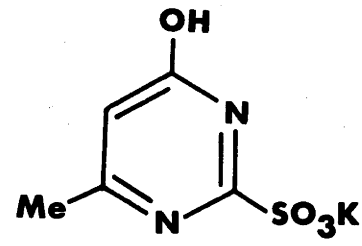


1.28

The 4-position of quinazoline is extremely reactive to nucleophilic attack and reacts with sodium bisulphite, or sulphurous acid, to give an adduct (1.23) (Higashino, 1960; Albert *et al.*, 1961). However when sodium bisulphite is allowed to react with quinazoline-3-*N*-oxide, sodium quinazoline-4-sulphonate (1.24) is formed; the 1-*N*-oxide does not react similarly (Higashino, 1961).

Some heterocyclic sulphonates have been prepared by metathesis. When a chloro compound is boiled under reflux with an aqueous solution of a sulphite a sulphonate is produced.

e.g. $$R\text{-}Cl + Na_2SO_3 \longrightarrow R\text{-}SO_3Na + NaCl$$

[*cf.* the reaction of sodium phenylsulphinate with 2-chloropyrimidine to obtain 2-phenylsulphonyl-pyrimidine (D.J. Brown and Ford, 1967).

$$Ph.SO_2.Na + 2\text{-}Cl\text{-}C_4H_3N_2 \xrightarrow[100^{o}/5h]{DMSO} 2\text{-}Ph.SO_2.C_4H_3N_2\ ].$$

Ochiai and Suzuki (1954) prepared sodium pyridine-4-sulphonate from the corresponding chloro compound by this method; Evans and H.C. Brown (1962) prepared also the 2-sulphonate similarly, although 3-chloropyridine was unaffected by the action of aqueous sulphite. Evans and H.C. Brown (1962) also found that 2-, 4-, and 6-chloro-pyridine-*N*-oxide reacted readily with sulphite to give the corresponding sulphonates, although reductive removal of the *N*-oxide occurred in the 2-isomer.

Sodium 2,4-dimethylpyrimidine-6-sulphonate (1.25) was prepared by Ochiai and Yamanaka (1955) using this method. They also submitted 2-chloropyrimidine and 2-chloro-4-methylpyrimidine to the same reaction but the resulting sulphonates were never purified. Sodium 8-hydroxy-6-mercaptopurine-2-sulphonate (1.26) was prepared from the corresponding 2-chloro compound (Elion *et al.*, 1959).

The most usual preparation of heterocyclic sulphonic acids is by oxidation of the corresponding thiols or disulphides. Sodium periodate oxidises 4-thiouracil nucleosides to the corresponding sulphonates, which undergo hydrolysis or ammonolysis to provide a useful route to uracil and cytosine nucleosides (Ziff and Fresco, 1968). Many pyrimidinesulphonic acids must have been made and immediately hydrolysed during the oxidative removal of mercapto groups with hydrogen peroxide, but relatively few have been isolated (D.J. Brown, 1962, p.295). Di(2,4-dimethoxypyrimidin-6-yl) disulphide has been oxidised with 30% hydrogen peroxide in the presence of formic acid to give the corresponding sulphonic acid (Greenbaum and Holmes, 1954). 2-Thiobenzimidazole has also been oxidised by peroxide to 2-sulphobenzimidazole (1.27) (Knobloch and Rintelen, 1958) and the same compound has been prepared by the addition of aqueous potassium permanganate to a boiling alkaline solution of the thione (Everett, 1930). The use of alkaline permanganate as an oxidant is also found in the preparation of potassium

purine-6-sulphonate by Doerr and co-workers (1961) and potassium 4-hydroxy-6-methylpyrimidine-2-sulphonate (1.28) by Levin and Kukhtin (1962). This latter compound was described as labile and its aqueous solution decomposed with the evolution of sulphur dioxide "even at 60-80°." This decomposition was accelerated markedly in the presence of acid. The sulphonate was converted by hydrazine hydrate (at 80° for a few minutes) into the 2-hydrazino compound.

Occasionally, the sulpho group in a heterocyclic sulphonic acid may be modified: for example, 2-sulphobenzimidazole is converted by chlorine into its 2-chlorosulphonyl derivative (Knobloch and Rintelen, 1958); such reactions are feasible only with sufficiently stable compounds.

Acid chlorides are more often made by the low temperature chlorination of a thione or related disulphide (Roblin and Clapp, 1950). The resulting heterocyclic sulphonyl chlorides are unstable. They decompose, rapidly when impure, to give the corresponding chloro compound by losing sulphur dioxide (Roblin and Clapp, 1950). Chloro compounds also result from such reactions carried out at higher temperatures: chlorine oxidation of 2-mercapto-5-nitropyridine gave 2-chloro-5-nitropyridine (Caldwell and Kornfeld, 1942), and 6-mercaptopurine (in absolute ethanol below 35°) gave 6-chloropurine (Hitchings and Elion, 1957; Wellcome Foundation. 1957). Sometimes

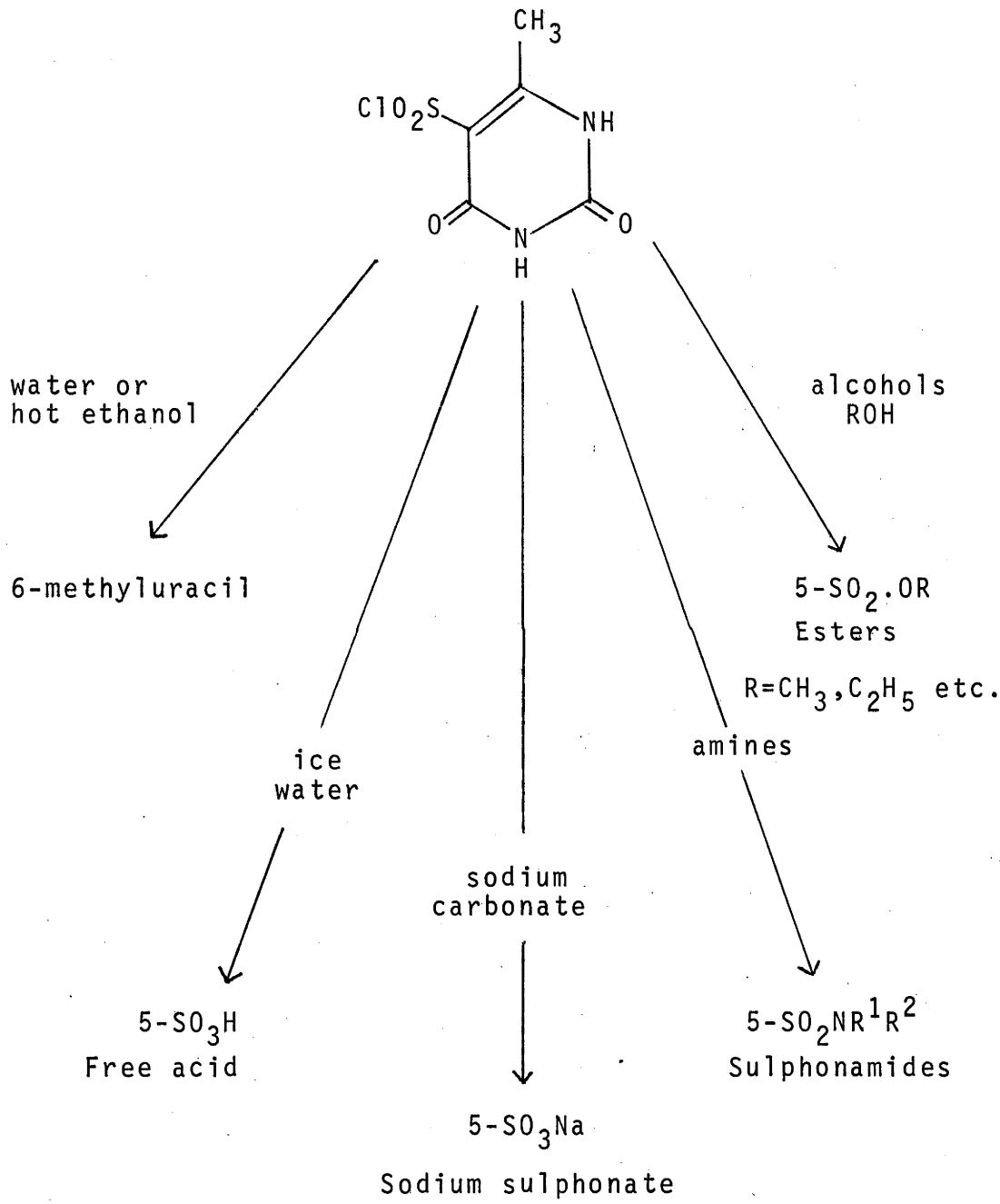
chlorine oxidation, even in non-aqueous media, gives the free acid rather than the acid chloride: Robins (1961) oxidised 8-hydroxypurine-2,6-thione in absolute methanol and obtained directly the corresponding disulphonic acid.

Sulphonyl chlorides react with alcohols under mild conditions to give esters (see chart p.16) but very few examples of this are known in heterocyclic chemistry although the reaction appears to be general in the carbocyclic aromatic field (Muth, 1955, p.663). Sulphonyl chlorides react with amines to give sulphonamides [*e.g.* those prepared by Pala (1958), who incidentally made his sulphonyl chlorides from thiols in the presence of ferric chloride; also those of Clapp and Roblin (1951) and Roblin and Clapp (1950); see also the chart on p.16]. Under gentle conditions sulphonyl chlorides may be hydrolysed to the free acid, or may react with alkali to give the corresponding sulphonates (see chart, p.16). The free acids are generally labile in the presence of mineral acids, or indeed in their own highly acidic aqueous solution (Levin and Kukhtin, 1962), being hydrolysed to the corresponding hydroxy compounds. They are less readily hydrolysed in alkali.

When benzenesulphonyl chloride is boiled for a short time with sodium or ammonium fluoride it is converted into benzenesulphonyl fluoride (Davies and Dick, 1931). Sulphonyl fluorides are found to be less reactive than sulphonyl chlorides, *e.g.* in their reactions with alcohols,

Reactions of 6-methyluracil-5-sulphonyl chloride

(Elderfield and Prasad, 1961)



water, and hydroxide ion (Swain and Scott, 1953); on the other hand they will undergo reactions, which the sulphonyl chlorides do not, because of their stability under more vigorous conditions,

$$e.g.\quad p\text{-}(CH_3)_2N.C_6H_4.SO_2F + HCO.NH.C_6H_5 \xrightarrow[200\text{-}220^{o}]{3h} p\text{-}(CH_3)_2N.C_6H_4.SO_2NH.C_6H_5$$

(Chechegoeva *et al.*, 1966). Since most N-heteroaromatic sulphonyl chlorides are rather unstable, the above method of conversion into sulphonyl fluorides is precluded by the vigorous conditions required. However it was found that a 2- or 6-purinethione may be oxidised with chlorine in the presence of a large excess of fluoride ion (under conditions which would normally give a sulphonyl chloride) to give a sulphonyl fluoride directly [Beaman and Robins, 1961; Beaman, 1963, (for purine-6-sulphonyl fluoride)]. These sulphonyl fluorides reacted with ammonia and amines to form sulphonamides and were hydrolysed in acid, alkali, or even water to the corresponding sulphonic acids or their salts. However the use of vigorous hydrolytic conditions caused rupture of the C-S bond and the formation of hydroxy compounds.

Beaman and Robins (1961) noticed that crude samples of such sulphonyl fluorides lost sulphur dioxide on standing; they speculated that this might provide a route to fluoro compounds by analogy with the observations of

Roblin and Clapp (1950) who had shown that a number of heteroaromatic sulphonyl chlorides spontaneously lost sulphur dioxide on standing at room temperature to give the corresponding chloro compounds. Likewise in the carbocyclic field *d*-camphor-π-sulphonyl bromides have been shown to lose sulphur dioxide when heated at 170^{o} to give high yields of the corresponding bromo compounds (Guha and Bhattacharyya, 1944). Since aryl fluorides cannot be prepared by direct halogenation [because of the inability of fluorine to form a cation and so take part in electrophilic attack (Olah and Kreienbühl, 1967)], such a preparation would be useful. It had been shown by Blum (1966) that an aromatic sulphonyl chloride underwent desulphonylation to the chloro compound when heated with chlorotris(triphenylphosphine)rhodium(I) and that this reaction was applicable to benzene, naphthalene, and related sulphonyl fluorides (Blum and Scharf, 1970; Olah and Kreienbühl, 1967). However no further report of the desulphonylation of heteroaromatic sulphonyl fluorides to the corresponding fluoro compounds has appeared.

Roblin and Clapp (1950) and Beaman and Robins (1961) prepared sulphonyl halides primarily as intermediates in the preparation of sulphonamides. They found that these sulphonamides were hydrolysed under acid conditions to give the corresponding hydroxy compounds and that they reacted under basic conditions to give sulphonates, presumably *via* hydration to the ammonium sulphonate.

E) Rate Studies of the Nucleophilic Displacement Reactions of Sulphonic Acids and Sulphonyl Halides.

In carbocyclic aromatic systems nucleophilic attack generally occurs only under extremely vigorous conditions: aryl metal sulphonates require fusion with sodium or potassium hydroxide, in the presence of water, at temperatures of 200-350^{o} for conversion into phenols (Buehler and Pearson, 1970). The addition of electron-withdrawing substituents (*e.g.* nitro) or the replacement of -CH= groups by nitrogen in such a system increases its reactivity remarkably towards nucleophilic attack. In a heteroaromatic system such as imidazole, in which the electron-release of one nitrogen (-NH-) has more influence over the system than the electron-withdrawal of the other (=N-) (Albert, 1968), the greater possibilities for resonance afforded in the cation and anion confer stability on both species. For similar reasons benzimidazole-2-sulphonic acid (1.27) is only slightly attacked by acid (heating with hydrochloric acid at 170^{o}/3h produces 7% hydrolysis) and it is stable to boiling for 2h in 25% sodium hydroxide (Everett, 1930). Similar stability in alkali, though not in acid, is also found in the purinesulphonic acids (Beaman and Robins, 1961) where dianion formation presumably stabilises the system against nucleophilic attack. As a result of this, all previous work in the carbocyclic field on the

solvolysis of sulphonyl halides has been concerned with the modification of this group rather than its replacement (*e.g.* Swain and Scott, 1953; Aberlin and Bunton, 1970; Rogne, 1971; Laird and Spence, 1971).

Several kinetic studies of displacements from N-heterocyclic systems have been carried out. These studies have concentrated mainly on the replacement of the *C*-chloro substituent by amines or alkoxide ion [*e.g.* Chapman and Russell-Hill (1956); Chapman and Rees (1954); also many examples in the review by Illuminati (1964); *cf.* analogous work by Biggi and Pietra (1971) on the replacement of chlorine in chloro-2,4-dinitrobenzene by amines]. Some more recent studies have examined the reaction of heteroaromatic sulphones and sulphoxides with amines (D.J. Brown and Ford, 1967), hydroxide ion (D.J. Brown and Ford, 1969), methoxide ion (Barlin and W.V. Brown, 1967 and 1968), and also the replacement of the trimethylammonio group by hydroxide ion (Barlin and Young, 1971).

No kinetic work on the nucleophilic displacement of the sulphonic acid or sulphonyl fluoride groups from heterocyclic nuclei has appeared prior to the present work.

CHAPTER 2

PREPARATIONS AND REACTIONS

A) Introduction

This Chapter describes the preparation and properties of simple pyrimidine-2-(and 4-)sulphonic acids, some of their *C*-methyl derivatives, and sulpho derivatives of some related bicyclic 1,3-diazines. In addition, a selection of derived sulphonyl halides and sulphonamides have been studied. Within this range of compounds the sulpho group proved to be of little use as a leaving group (*cf.* D. J. Brown, 1970, p.222-223). However the fluorosulphonyl group was found to be a good leaving group; in addition, its modification by amines furnished an improved synthesis of the corresponding sulphonamides. Some disulphides and a sulphenamide are also described.

B) Compounds Related to Sulphenic Acids

Mild oxidation of heteroaromatic thiones (thiols) to derivatives of sulphenic acid does not affect the oxidation state of sulphur. Two classes of related compounds were prepared: a sulphenamide and several disulphides.

4,6-Dimethylpyrimidine-2-thione in potassium hydroxide solution was oxidised below 0^{o} by similarly cooled aqueous chloramine to give 4,6-dimethylpyrimidine-2-sulphenamide (2.1; X = SNH_2)(*cf.* Hurley and Robinson, 1965) which crystallised when the solution was allowed to warm to room temperature. The compound was made in the hope of finding another practical route to simple

pyrimidinesulphonamides (*cf.* Greenbaum, 1954). However, when an aqueous ethanolic solution of the sulphenamide was oxidised by dropwise addition of neutral aqueous potassium permanganate, only a very small amount of di(4,6-dimethylpyrimidin-2-yl) disulphide (2.2) could be isolated from the reaction mixture. [The formation of this compound under such conditions supports the speculations of Sisler *et al.* (1970) that the disulphides formed by chloroamination of thiols may arise *via* the sulphenamides.] The mother liquor was shown by t.l.c. to contain a minute amount of the expected sulphonamide (2.1; X = SO_2NH_2) along with more disulphide. The very low yield of both products indicated that further oxidative and/or hydrolytic reactions must have occurred. Several other oxidising agents were tried on the sulphenamide. It was unchanged by mild treatment with 3% hydrogen peroxide, *m*-chloroperoxybenzoic acid in chloroform, or potassium permanganate in acetone; 30% hydrogen peroxide in acetone or acetic acid, followed by neutralisation with ammonia gave a crude product clearly containing ammonium 4,6-dimethylpyrimidine-2-sulphonate from its i.r. spectrum, but no sulphonamide could be isolated. Treatment of 4,6-dimethylpyrimidine-2-thione with diethylchloramine under the conditions used above gave only di(4,6-dimethylpyrimidin-2-yl) disulphide (2.2). This disulphide was also obtained from the oxidation of the thione with potassium permanganate in acetone (an

excellent method of preparation) and by the oxidation of an alkaline solution of the thione with iodine. The latter method was also used for the preparation of di(4-methylpyrimidin-2-yl) disulphide, its 5-methyl isomer, and dipyrimidin-2-yl disulphide. However because of the lability of these disulphides in alkali, the reaction was successful only at *ca* pH 7 [*cf.* Doerr *et al.* (1961) who prepared some purin-6-yl disulphides].

Quinazoline-2-thione was oxidised by iodine to the corresponding disulphide; the yield was low, probably because of the very low solubilities of both thione and disulphide. Oxidation of the thione by potassium permanganate in acetone was even less successful: only a crude product, shown by mass spectrometry to contain the disulphide, was obtained. Similar oxidation of quinazoline-4-thione gave only a small amount of unchanged starting material: the large amount of potassium permanganate required for the reaction indicated breakdown of the quinazoline ring.

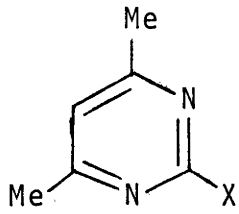
Although purine-2-thione was stable to potassium permanganate in boiling acetone, in a hot aqueous solution at pH 8 it did react with iodine: no disulphide could be isolated. Purine-8-thione was oxidised by both reagents, but again no disulphide could be isolated. 4,5-Diaminopyrimidine-2-thione was found to be stable both in aqueous iodine and in an acetone solution of potassium permanganate.

C) Compounds Related to Sulphonic Acids

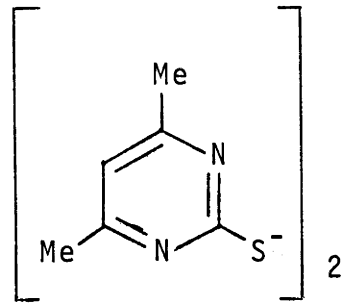
1) Preparation of Sulphonates

Ten potassium pyrimidinesulphonates [2.3(a-e) and 2.4(b-f)] were prepared by boiling the corresponding chloropyrimidines in aqueous potassium sulphite for the minimum time consistent with complete displacement of each chloro substituent; longer reaction times caused progressive hydrolysis of the product, as did any variation from an optimum initial pH of 7. When 4-chloro-2-methylpyrimidine was boiled with a slightly acidic solution of sulphite (pH *ca* 5) the only product isolated was the corresponding pyrimidinone. In the preparation of potassium 2,4-dimethylpyrimidine-6-sulphonate (2.4.d), 2,4-dimethylpyrimidin-6-one was isolated from the mother liquors. Even at pH 7 hydrolysis was a serious competing (or subsequent) reaction in the preparation of the unsubstituted potassium pyrimidine-2-sulphonate (2.3.a): an analytically pure sample, uncontaminated by pyrimidin-2-one could not be obtained by this method. 4-Chloropyrimidine and its 5-methyl homologue were too unstable (half-lives of a few minutes) to undergo the reaction.

The choice of potassium sulphite was made after preliminary experiments with potassium, sodium, and lithium sulphite; the selection was limited by the insolubility of other readily available metal sulphites.



2.1



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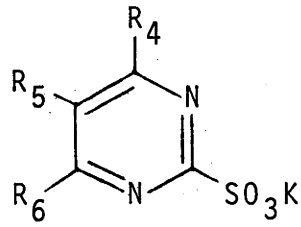

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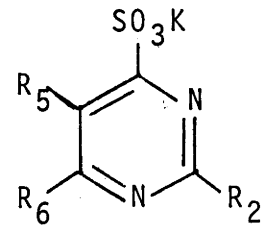


2.4

	R_4	R_5	R_6
a	H	H	H
b	Me	H	H
c	H	Me	H
d	Me	H	Me
e	Me	Me	H

	R_2	R_5	R_6
a	H	H	H
b	Me	H	H
c	H	H	Me
d	Me	H	Me
e	H	Me	Me
f	Me	Me	Me

The potassium pyrimidinesulphonates proved least troublesome to separate from the inorganic salts present in the reaction mixtures. Even so, several such sulphonates could not be separated from non-stoichiometric proportions of potassium chloride (see Experimental, Chapter 5): repeated recrystallisation or variation within the limited range of useful solvents (water and the lower alcohols) effected no improvement, often the reverse. Because of the alkalinity of its solution, commercial potassium sulphite was unsatisfactory for these preparations. Accordingly, a sample of potassium sulphite was prepared which by its neutral solution and method of preparation must have contained some bisulphite (*cf.* Durrant and Durrant, 1962; Parkes and Mellor, 1939). This material was unstable (shelf-life *ca* 3 months), but it was satisfactory for metathesis.

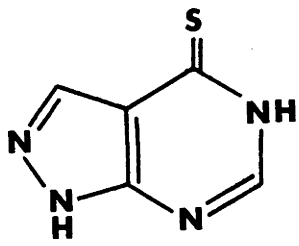
Ultimately it was found more convenient to prepare the pyrimidinesulphonates by oxidation of appropriate thiones. 4,6-Dimethylpyrimidine-2-thione in aqueous ethanol was oxidised cleanly by neutral aqueous potassium permanganate solution to give the corresponding sulphonate. This process was a marked improvement over the metatheses described above and was applied with equal success to the preparation of some other pyrimidine, purine, and quinazoline sulphonates. At the end of an oxidation the reaction mixture was still neutral; after removal of manganese dioxide, the filtrate contained only the

desired sulphonate free from any inorganic impurities. By this method the previously unobtainable potassium pyrimidine-4-sulphonate (2.4.a) was prepared; also some other sulphonates, hitherto obtained only as specimens contaminated with potassium chloride.

In the pyrimidine series, it was found that the least soluble salt was potassium 2,4-dimethylpyrimidine-6-sulphonate (*cf.* Ochiai and Yamanaka, 1955) and the most soluble were potassium 2,4,5-trimethyl- and 4-methyl-pyrimidine-6-sulphonates. The very soluble compounds were naturally the most difficult group to purify from potassium chloride by crystallisation.

Oxidation of purine-2-thione was extremely slow at room-temperature: no product identifiable as potassium purine-2-sulphonate could be isolated from reactions carried out at temperatures from 0^{o} to 100^{o}. Similarly no identifiable products were obtained from the oxidation of pyrazolo[3,4-*d*]pyrimidine-6-thione (2.5) or 3,4,5,6,7,8-hexahydroquinazoline-2-thione (2.6). (Kindly supplied by Dr W.L.F. Armarego).

Oxidation of pyrimidine-2-thione with *m*-chloro-peroxybenzoic acid [the reagent of choice in the preparation of many heteroaromatic sulphoxides or sulphones from the corresponding thioethers (see for example D.J. Brown and Ford, 1967)] gave no identifiable product.



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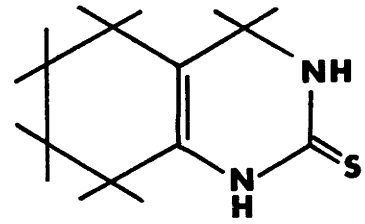

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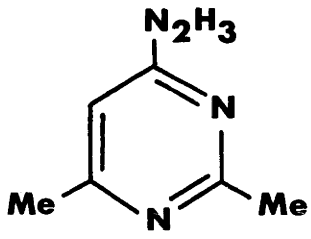

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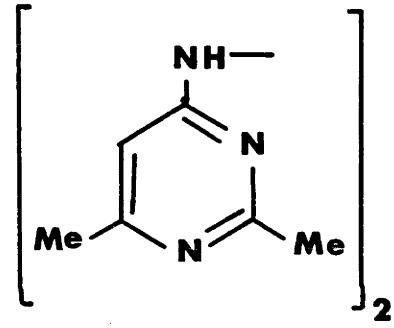

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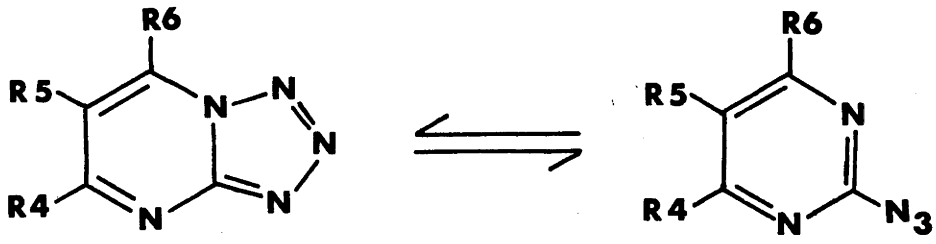


a) R4 and R6 = Me; R5 = H

b) R4 and R6 = H ; R5 = Me

2.9

2) Preparation of Sulphonyl Halides

Pyrimidinesulphonyl chlorides had been shown by Roblin and Clapp (1950) to be among the least stable of a series of heterocyclic sulphonyl chlorides. This instability was confirmed during the preparation of 4,6-dimethyl-2-sulphamoylpyrimidine by their method: the loss of sulphur dioxide from the crude pyrimidinesulphonyl chloride intermediate was very obvious and the residue smelt strongly of chloropyrimidine. The spontaneous decomposition of sulphonyl chlorides precluded an examination of such compounds, but the experience of Beaman and Robins (1961) in the purine series suggested that simple pyrimidinesulphonyl fluorides might prove more amenable to study. Accordingly a well-cooled slurry of 4,6-dimethylpyrimidine-2-thione and potassium hydrogen difluoride in aqueous methanol was submitted to a stream of chlorine. [The acid fluoride salt was found preferable to potassium fluoride: reactions in which it was used gave a purer product. It has been claimed (Beaman and Robins, 1961) that the acid fluoride "provides a buffered reaction medium in which it keeps the acidity low and prevents acid-catalysed nucleophilic replacement of the entire chlorosulphonyl group," but this reasoning seems open to doubt!]. The 4,6-dimethylpyrimidine-2-sulphonyl fluoride (2.1; X = SO_2F) which resulted in good yield, was a low melting solid, stable to recrystallisation from boiling ethanol and to

keeping under laboratory conditions for at least a year. Other thiones were oxidised similarly to give pyrimidine-2-sulphonyl fluoride, its 4- and 5-methyl homologues, quinazoline-2-sulphonyl fluoride, and the known purine-6-sulphonyl fluoride (Beaman and Robins, 1961). Attempts to similarly oxidise the following compounds failed because of the instability of the products: 2,4-dimethylpyrimidine-6-thione (from which an unstable oil, smelling of a chloropyrimidine was obtained; within 24h the smell disappeared and the residue became completely soluble in water), pyrazolo[3,4-*d*]pyrimidine-6-thione (a small quantity of the corresponding pyrazolopyrimidin-6-one was isolated from the reaction mixture), quinazoline-4-thione, and purine-8-thione. [In contrast the last two compounds are readily oxidised by aqueous permanganate to the corresponding potassium sulphonates and 2,4-dimethyl-pyrimidine-6-thione would probably react similarly (*cf.* preparation of its 4-methyl homologue)].

3) Metatheses and Reactions of the Sulphonates

When a solution of potassium 2,4-dimethylpyrimidine-6-sulphonate (2.4.d) was passed through a column of Dowex 50W ion-exchange resin (in its acid form but exhaustively washed with water until the eluate had a pH of 5) the acidity of the eluate increased to *ca* pH 1.5 showing the presence of free pyrimidinesulphonic acid. A similar column, containing resin in the ammonium form, gave a

crude sample of ammonium 2,4-dimethylpyrimidine-6-sulphonate (as judged from its i.r. spectrum) which decomposed on heating: no compound identifiable as a sulphonamide could be isolated from the pyrolysis residue.

Dry distillation of sodium 2,4-dimethylpyrimidine-6-sulphonate with potassium cyanide yields the corresponding cyano compound (Ochiai and Yamanaka, 1955). When a mixture of the two potassium salts in dimethylformamide was boiled under reflux for 2h the resulting mixture (after purification, finally by chromatography on alumina with benzene) gave a very small amount of oil which contained (from its i.r. spectrum) a cyano compound; the use of pyridine as a solvent gave a similar result. A pure sample of 4-cyano-2,6-dimethylpyrimidine could not be obtained from the crude products.

With the exception of purine-6(and 8)-sulphonates, which are stable in alkali, all the sulphonates prepared were hydrolysed in both hydrochloric acid and aqueous sodium hydroxide solution to give the corresponding hydroxy compounds (see Chapter 3 for rate studies). Replacement of the sulpho by a hydrazino group occurred when a potassium sulphonate in hydrazine hydrate was boiled under reflux for at least 30 min (*cf.* Evans, 1962). Potassium 4,6-dimethylpyrimidine-2-sulphonate (2.3.d) and the isomeric potassium 2,4-dimethylpyrimidine-6-sulphonate (2.4.d) gave the corresponding hydrazino compounds (2.1; X = N_2H_3 and 2.7) in 40-60% yield depending on

conditions. When the concentration of free hydrazine was restricted during the preparation of 4-hydrazino-2,6-dimethylpyrimidine (by using a neutral mixture of hydrazine and hydrazine sulphate), in the unrealised hope of detecting an intermediate sulphonohydrazide, the *NN*'-bis-2,4-dimethylpyrimidin-6-ylhydrazine (2.8) was obtained as a by-product (see Chapter 4 for its mass spectrum). Potassium quinazoline-4-sulphonate reacted with hydrazine hydrate to give a low yield of the hydrazino compound; even after sublimation, it was shown by mass spectrometry to contain a little of the corresponding quinazolinone. The pure amine was obtained by repeated crystallisation from ethanol.

4) Metatheses and Reactions of the Sulphonyl Fluorides

Sulphonyl fluorides undergo metathesis either by replacement of the fluorine atom or by rupture of the C-S bond and complete displacement of the fluorosulphonyl group.

On dissolution in liquid ammonia, 4,6-dimethylpyrimidine-2-sulphonyl fluoride was converted rapidly into the corresponding sulphonamide (2.1; X = SO_2NH_2), identical with a specimen prepared by modification of the known procedure (Roblin and Clapp, 1950); pyrimidine-2-sulphonamide and also its 4- and 5-methyl derivatives were made similarly. The sulphonyl fluoride (2.1; X = SO_2F) reacted under mild conditions with appropriate

amines to give the 4,6-dimethylpyrimidine-2(*N*-substituted)-sulphonamides [2.1; X = SO_2NHEt, SO_2NEt_2, $SO_2NPr^i_2$, $SO_2N(CH_2.CH_2)O$, or $SO_2NH.NH_2$ (*cf.* Evans, 1962)]; the last of these was characterised additionally as its isopropylidene derivative (2.1; X = $SO_2NH.N{:}CMe_2$). In contrast, quinazoline-2-sulphonyl fluoride reacted with diethylamine under similar conditions to give 2-diethylaminoquinazoline, isolated as its picrate.

4,6-Dimethylpyrimidine-2-sulphonyl fluoride did not react with a number of substituted hydrazines: *p*-toluenesulphonohydrazide [which converts 4-chloroquinazoline to 4-(*N*'-toluene-*p*-sulphonohydrazido)quinazoline (Armarego, 1962)], thiosemicarbazide, 2,4-dinitrophenylhydrazine, and *N*-(4-methoxy-5-nitropyrimidin-6-yl)-*N*-methylhydrazine. In reactions with aniline, 2-aminopyridine, and sodium sulphanilamate only unresolved complex mixtures were obtained.

No other reactions tried led solely to modification of the fluorosulphonyl group. Boiling a mixture of 4,6-dimethylpyrimidine-2-sulphonyl fluoride, zinc oxide, and pyridine in methanol for 1h (*cf.* Rogne, 1971; Muth, 1955, p.666) gave on filtration and evaporation only unchanged starting material instead of the expected ester; when purine-6-sulphonyl fluoride in ethanol was boiled under reflux for 18h (conditions which have little effect on the above pyrimidinesulphonyl fluorides) a

mixture of compounds was obtained which could not be resolved.

Under conditions more vigorous than those used for the preparation of the corresponding sulphonamides, the whole 2-substituent of the pyrimidine-2-sulphonyl fluorides underwent nucleophilic displacement. 4,6-Dimethylpyrimidine-2-sulphonyl fluoride and its 5-methyl homologue gave the corresponding hydrazino compounds when boiled for a few minutes with hydrazine hydrate; likewise the reaction of the fluoride with diethylamine in a sealed tube at 150° for 4h gave 2-diethylamino-4,6-dimethylpyrimidine.

In an attempt to prepare a sulphonazide, 4,6-dimethylpyrimidine-2-sulphonyl fluoride and sodium azide in aqueous methanol were warmed to give (on purification) the 2-azidopyrimidine (2.1; X = N_3). Purification of the mother liquors by preparative t.l.c. gave 4,6-dimethyl-2-sulphamoylpyrimidine (2.1; X = SO_2NH_2) in addition to the azidopyrimidine. The presence of sulphonamide indicated that a sulphonazide had been formed (Breslow, 1970) [*cf.* comments on the Curtius and Schmidt reactions by Smith (1946)] and that it had decomposed spontaneously with loss of nitrogen to a nitrene which then protonated: "In no case has the source of the hydrogen atoms been identified."(Breslow). A similar reaction of 5-methylpyrimidine-2-sulphonyl fluoride with sodium azide gave the corresponding azido compound, and a low yield of another unstable compound,

which was not the sulphonamide. The above azidopyrimidines are in tautomeric equilibrium with 5,7-dimethyl- and 6-methyltetrazolo[1,5-*a*]pyrimidine respectively (2.9) (Temple and Montgomery, 1965; Wentrup, 1970)(see n.m.r. spectra in Chapter 4).

When boiled in water, 4,6-dimethylpyrimidine-2-sulphonyl fluoride slowly hydrolysed to the corresponding pyrimidinone; in methanolic sodium methoxide it gave the corresponding 2-methoxypyrimidine. The other pyrimidine-sulphonyl fluorides behaved similarly with methanolic sodium methoxide (see Chapter 3 for the rates of these reactions). When purine-6-sulphonyl fluoride in methanolic sodium methoxide was boiled for 3h it gave (after addition of water and neutralisation) a crude sample of sodium purine-6-sulphonate (*cf.* Huber, 1957, who prepared 6-alkoxypurines by the action of alkoxides on 6-chloropurine).

Fusion of 4,6-dimethylpyrimidine-2-sulphonyl fluoride with potassium cyanide, or boiling these compounds together in a variety of solvents did not give the corresponding cyanopyrimidine.

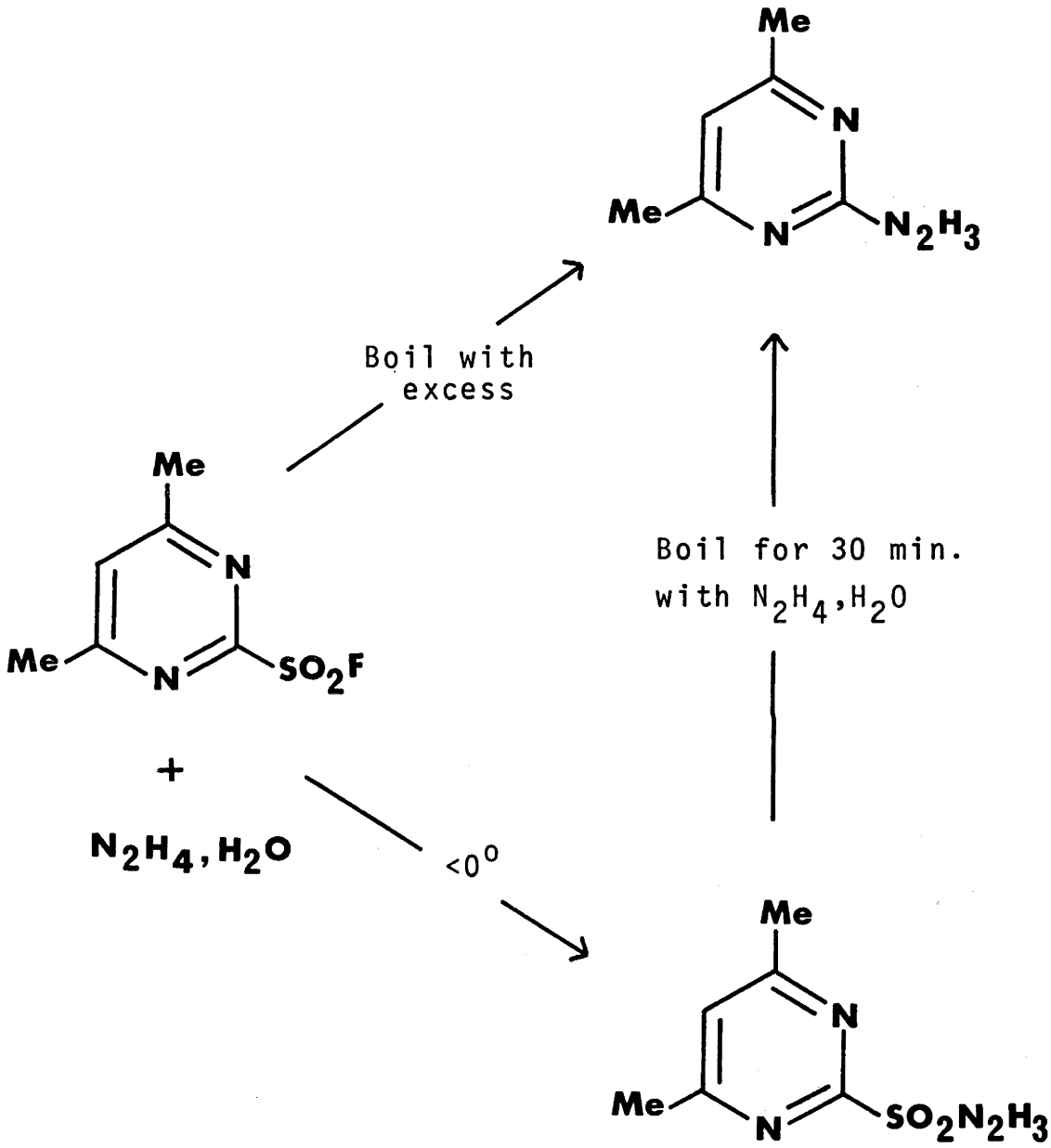
When the sulphonyl fluoride in dimethyl- or diethyl-formamide was boiled, only very small yields of the corresponding dialkylaminopyrimidines were obtained (by t.l.c.)(*cf.* Heindel and Kennewell, 1969).

Many unsuccessful attempts were made to desulphonate 4,6-dimethylpyrimidine-2-sulphonyl fluoride to the

corresponding fluoro compound. It was unchanged when (melted and) boiled under reflux, either alone, in the presence of potassium fluoride, or when its solution in anhydrous diethyl ether, or light petrol, was boiled with silver fluoride [*cf.* Beaman and Robins (1963) who used the reaction of 6-chloro-9-methylpurine with silver fluoride to obtain the corresponding fluoro compound]. Extensive decomposition to a complex mixture occurred on heating with chlorotris(triphenylphosphine)rhodium(I) (kindly supplied by Dr M.A. Bennett, Research School of Chemistry) under a variety of conditions (*cf.* Blum and Scharf, 1970).

5) Metatheses and Reactions of the Sulphonamides

4,6-Dimethyl-2-sulphamoylpyrimidine underwent extensive decomposition when boiled in aqueous methanol with Raney nickel: no corresponding sulphenamide, hydroxy compound, or starting material could be detected in the resulting mixture. This sulphonamide, and the derived sulphonohydrazide, underwent nucleophilic displacement when boiled with hydrazine hydrate to give the corresponding 2-hydrazino compound. Such reactions indicate that when amines react with sulphonyl fluorides to give amino compounds (rather than sulphonamides) these amino compounds can be formed *via* intermediate sulphonamides. It is possible that this route occurs preferentially to direct nucleophilic displacement of the fluorosulphonyl group itself (2.10).


Me
N
Me
N
N_2H_3
Boil with
excess
Me
N
Me
N
SO_2F
+
N_2H_4, H_2O
Boil for 30 min.
with N_2H_4, H_2O
<0°
Me
N
Me
N
$SO_2N_2H_3$

2.10

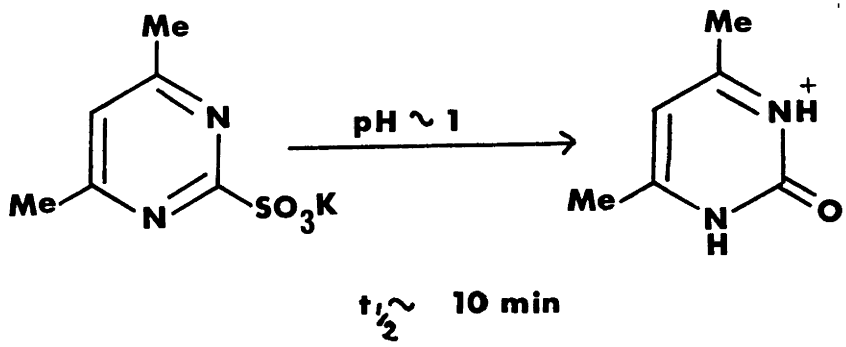
CHAPTER 3

RATE STUDIES

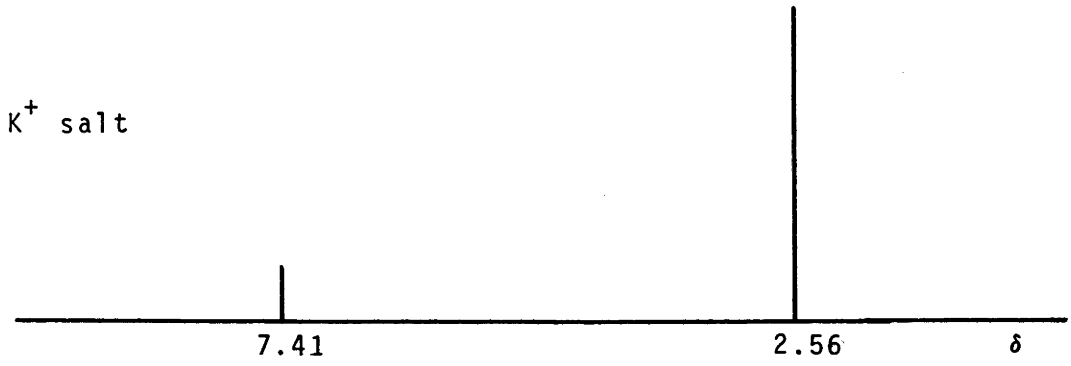
In order to obtain a better understanding of the observed chemical properties of the pyrimidinesulphonates, their rates of hydrolysis were measured. This study prompted the preparation of some sulphonates of two related heterocyclic systems.

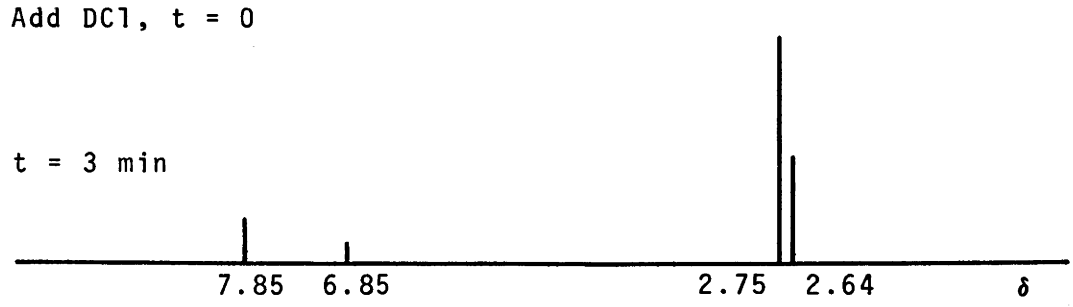
Preliminary experiments revealed that the sulphonates were reasonably stable as anions at pH 7 (the u.v. spectra of aqueous solutions of some pyrimidinesulphonates were unchanged after standing under laboratory conditions for 3 months) but that they hydrolysed rapidly as anions (with the exception of the 6- and 8-purinesulphonates) in strong alkali, or as neutral molecules or zwitterions in strongly acidic solutions, to give only the corresponding oxo compounds. 4,6-Dimethylpyrimidin-2-one was isolated from hydrolytic reactions in both acid and alkali for identification with authentic material; the identities of other products were checked by comparing the u.v. spectra of their solutions (reaction mixtures after at least 5 x $t_{\frac{1}{2}}$) with those of appropriate authentic specimens under comparable conditions; in some cases, n.m.r. spectra (3.1; and Table 4.D.1) were also compared for confirmation.

Initial rate studies were carried out using n.m.r. spectroscopy. These experiments confirmed the suspected course of each reaction and gave an order of magnitude for its rate. The method was limited by the facile hydrolysis of the compounds which made it impossible to prepare reaction mixtures of known composition at a known



$t_{1/2} \sim$ 10 min





3.1

temperature and to measure their spectra in the early stages of the hydrolysis. Also due to the low accuracy of electronic integration (on the available instrument), the errors associated with integration of the peaks by weighing, and the errors inherent in using the peak heights as a measure of the concentration, the results so obtained were clearly far less accurate than those obtainable by u.v. spectroscopy. Accordingly all reaction rates (Tables 3.1 - 3.4) were determined by observing changes in u.v. absorption at a fixed wavelength with time. The rapidity of hydrolysis necessitated the use of a stopped-flow rapid-reaction apparatus (see Experimental. Chapter 5) to measure the rates of all the acidic and most of the alkaline hydrolyses. Because of the low(pK_a *ca* 0) dissociation constants of the sulphonates (Chapter 4, section C), acidic hydrolyses were carried out in strongly acidic solutions to ensure that only one species (neutral molecule or zwitterion) would be present. However, the exothermic dilution of strong acids in the rapid-reaction apparatus precluded the use of solutions more acidic than H_0 -1, *i.e.* a 1 : 1 dilution of 5.9 M-hydrochloric acid. Consequently, the acidic hydrolysis of a number of compounds could not be studied in practice (the rates of acidic hydrolysis of the pyrimidine-2-sulphonates were measured before the determination of their dissociation constants).

Table 3.1

Rates of Acidic Hydrolysis

Pyrimidine	Temp.[a] (°C)	Anal.λ (nm)	kx10^5 [b] [c] (s^{-1})		$t_{½}$ [c] (min)
2-sulphonic acids					
4-Me	25	302	*139*	(92)	*8.35*
4,6-Me_2	25	315	*359*	(75)	*3.23*
6-sulphonic acids					
2-Me	25	273	*547*	(79)	*2.12*
4-Me	25	230	*109*	(70)	*10.6*
2,4-Me_2	25	230	*120*	(74)	*9.63*
4,5-Me_2	25	238	*41.3*	(63)	*28.0*
2,4,5-Me_3	25	237	*87.5*	(85)	*13.2*

[a] Thermostatted to ± 0.1°.

[b] Reaction followed from <10% to % in parenthesis.

[c] Acidic hydrolysis (2.85M-hydrochloric acid).

Table 3.2

Rates of Alkaline Hydrolysis

Pyrimidine	Temp.[a] (°C)	Anal.λ (nm)	k x 10^5 [b] [c] (s^{-1})		$t_{½}$ [c] (min)
2-sulphonic acids					
unsubst.	40	292	93.9	(93)	12.3
	25	292	26.1	(77)	44.2
4-Me	40	288	27.5	(96)	42.0
	25	290	8.34	(82)	139
5-Me	40	304	5.26	(91)	220
$4,5\text{-Me}_2$	40	300	1.40	(94)	828
$4,6\text{-Me}_2$	40	288	8.83	(92)	131

Table 3.2 contd.

6-sulphonic acids					
unsubst.	40	232	275	(*ca.* 100)	4.2
	25	232	77.9	(91)	14.8
2-Me	40	273	98.8	(97)	11.7
	25	273	30.3	(87)	38.2
4-Me	40	273	58.0	(98)	19.9
2,4-Me_2	40	273	21.6	(96)	53.5
4,5-Me_2	40	273	4.63	(92)	249
2,4,5-Me_3	40	232	1.90	(79)	609

[a] Thermostatted to ± 0.1°.

[b] Reaction followed from <10% to % in parenthesis.

[c] Alkaline hydrolysis (1.00M-sodium hydroxide).

Table 3.3

Rates of Hydrolysis

Compound	Temp.[a] (°C)	Anal.λ (nm)	k x 10^5 [b,c] (s^{-1})	$t_{½}$ [c] (min)
Purine				
6-SO_3K	25	245	*734* (98)	*1.57*
9-Me-6-SO_3K	25	250	*802* (100)	*1.44*
	40	250	483 (96)	2.39
8-SO_3K	25	285	*272* (100)	*4.25*
Quinazoline				
2-SO_3K	40	360	82 (100)	14.07
H_4-4-SO_3K	25	240	*151* (99)	*7.65*
	40	240	16 (96)	70.53
H_4-2-Me-SO_3K	25	240	*300* (100)	*3.85*
	40	240	6 (84)	189.1

[a] Thermostatted to ±0.1°.

[b] Reaction followed from <10% to % in parentheses.

[c] Values in Roman type refer to alkaline hydrolysis (1.00M-sodium hydroxide); those in italics to acidic hydrolysis (2.85M-hydrochloric acid).

Table 3.4

Formation rates of 2-methoxypyrimidines from pyrimidine-2-sulphonyl fluorides in an excess of methanolic 0.051M-sodium methoxide at 25°.[a]

Pyrimidine	Anal.λ (nm)	k x 10^3 [b] (s^{-1})	$t_{½}$ (s)
2-SO_2F	265	46.9 (88)	15
4-Me-2-SO_2F	265	11.7 (68)	59
5-Me-2-SO_2F	272	3.57(74)	194
4,6-Me_2-2-SO_2F	265	3.58(90)	193

[a] Thermostatted to ±0.1°.

[b] Reaction followed from <10% to % in parentheses.

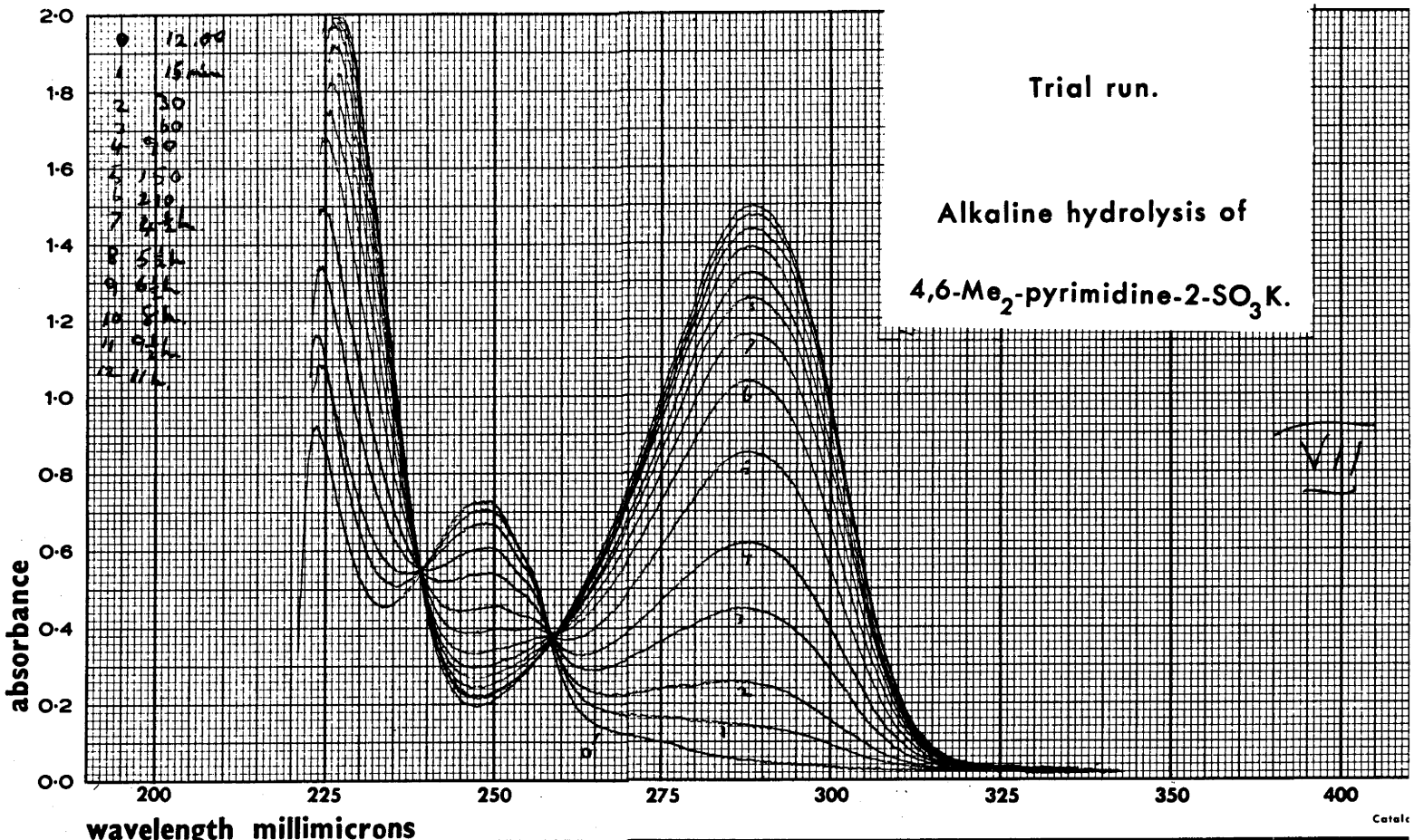
A preliminary study was made of each reaction using an automatic recording spectrometer; successive scans from 220 to 320 nm at fixed time intervals showed isosbestic points and revealed where the difference in absorption of the reactant and product was maximal. This wavelength was used for analytical purposes; where possible the analytical wavelength was chosen at a point where one species (reactant or product) had no absorption and the other species had an absorption maximum (3.2) [concentration of the absorbing species was directly proportional to the absorption: Hammett (1970)]. Frequently, however, an analytical wavelength had to be chosen where both species absorbed (3.3): under such conditions the combined absorption was linearly related to the concentration (Hammett, 1970). This resulted in undue emphasis being placed on the 'infinity' value of the absorption which was generally measurable with less reliability than other absorption values. To counteract this, the reaction rate (k) was calculated by Guggenheim's method and earlier results that had been calculated from the first-order rate equation {$kt = \log[a/(a - x)]$} were checked (see Appendix).

The hydrolyses were followed at the analytical wavelength either on an automatic recording instrument or (for the slower alkaline hydrolyses) on a manual instrument. Alkaline hydrolyses were carried out at pH 14.0. After determination of the pK_a values for

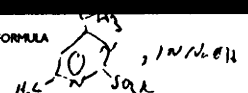
ULTRAVIOLET SPECTROPHOTOMETER

UNICAM SP.800

Chart supplied by Recorder Charts (Aust.



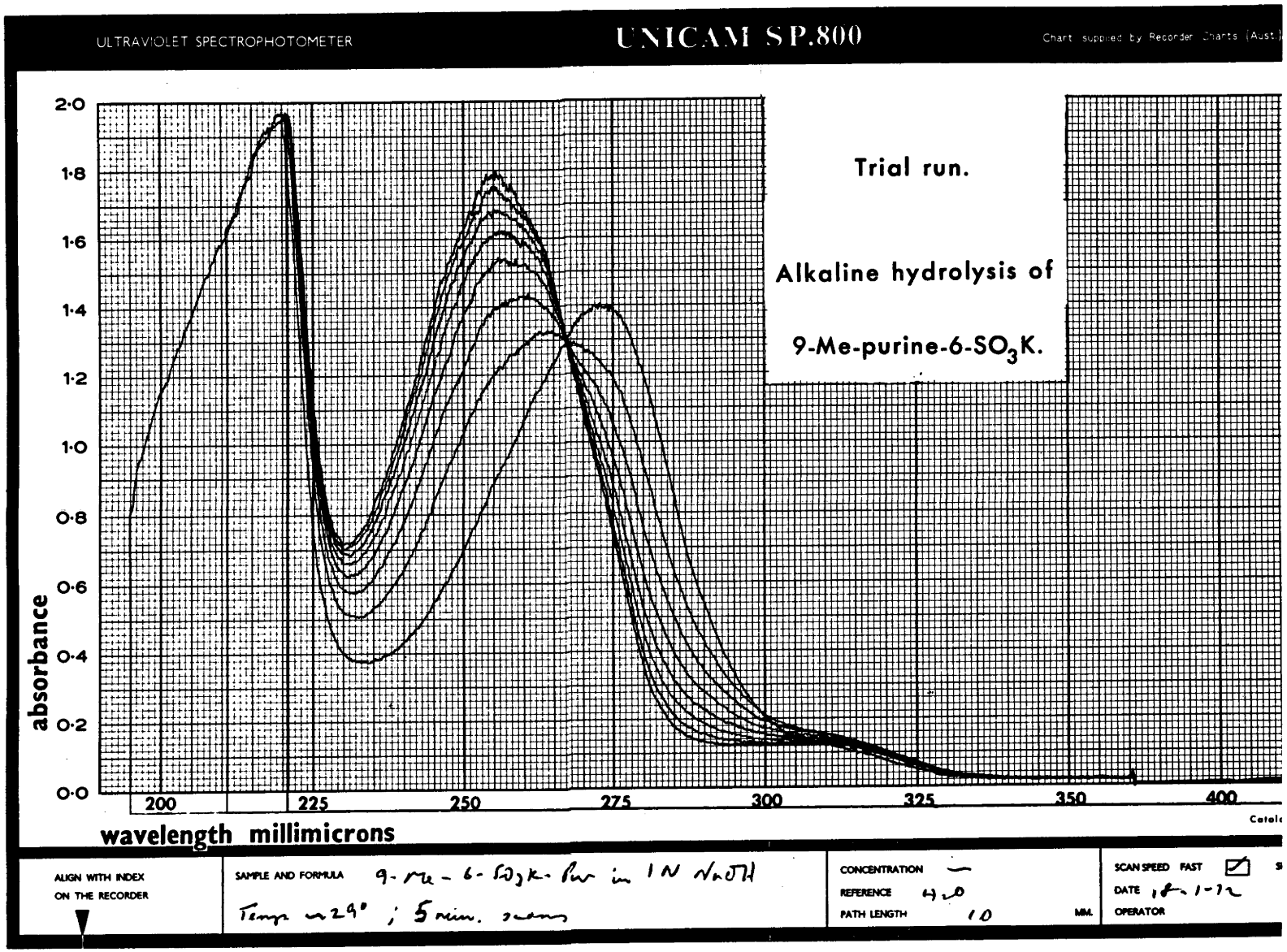
ALIGN WITH INDEX ON THE RECORDER

SAMPLE AND FORMULA  , 1N NaOH

4,6-Dimethyl-2-sulphonic pyrimidine (K⁺ salt)
in 1ml N. NaOH

CONCENTRATION 57.25 mg/l.
REFERENCE 1N NaOH
PATH LENGTH 10 MM.

SCAN SPEED FAST [V]
DATE 11/2/71
OPERATOR


ULTRAVIOLET SPECTROPHOTOMETER
UNICAM SP.800
Chart supplied by Recorder Charts (Aust.)
Trial run.
Alkaline hydrolysis of
9-Me-purine-6-SO3K.
absorbance
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
200
225
250
275
300
325
350
400
wavelength millimicrons
ALIGN WITH INDEX ON THE RECORDER
SAMPLE AND FORMULA 9-Me-6-SO3K-Pur in 1N NaOH
Temp 29° ; 5 min. scans
CONCENTRATION —
REFERENCE H2O
PATH LENGTH 10 MM.
SCAN SPEED FAST
DATE 18-1-72
OPERATOR

3.3

48

gain of a proton by the anions (see Chapter 4, section C), acidic hydrolyses were measured at H_0 -1. At this acidity the purine- and reduced quinazoline-sulphonates were present as neutral molecules or zwitterions; the pyrimidine-6-sulphonates all contained not more than 5% anion; and potassium 4-methyl- and 4,6-dimethylpyrimidine-2-sulphonates contained *ca* 35% and *ca* 11% anion respectively (see above). The 6- and 8-purinesulphonates were stable as their dianions at pH 14.0 [see pK_a values in Chapter 4, section C; similar examples of such resistance to nucleophilic displacement can be found in the book by Lister (1971)]. Potassium quinazoline-4-sulphonate was hydrolysed too rapidly for measurement of its pK_a or rates of hydrolysis. It was completely hydrolysed by acid (2.85M-hydrochloric acid) in 3 sec and at about one tenth this rate in alkali (1N-sodium hydroxide).

Comparing the alkaline hydrolyses at 40° (Tables 3.2 and 3.3), the pyrimidine-4-sulphonates (including the two tetrahydroquinazolinesulphonates) were 2-3 times more reactive than their 2-isomers and the deactivating effect of each added methyl group was considerable: each 2-, 4-, or 6-methyl group decreased the rate by a factor of 3-4; a 5-methyl group by a factor of 12-20. The reduced quinazolines were about three times more reactive than the corresponding pyrimidines which may reflect the steric difference between a constrained methylene and a

free methyl group. Repetition of some of the hydrolyses at 25° indicated that the rates doubled approximately for a 10° rise in temperature. On the available data for acidic hydrolyses at 25°, differences between the 2- and 4-pyrimidinesulphonates were rather less marked than above; so too was the effect of each methyl group especially at the 5- position. In addition there was an anomalous rate-enhancing effect of the 2-methyl group, possibly a further indication that protonation occurs on an (adjacent) ring nitrogen (see Chapter 4, section C).

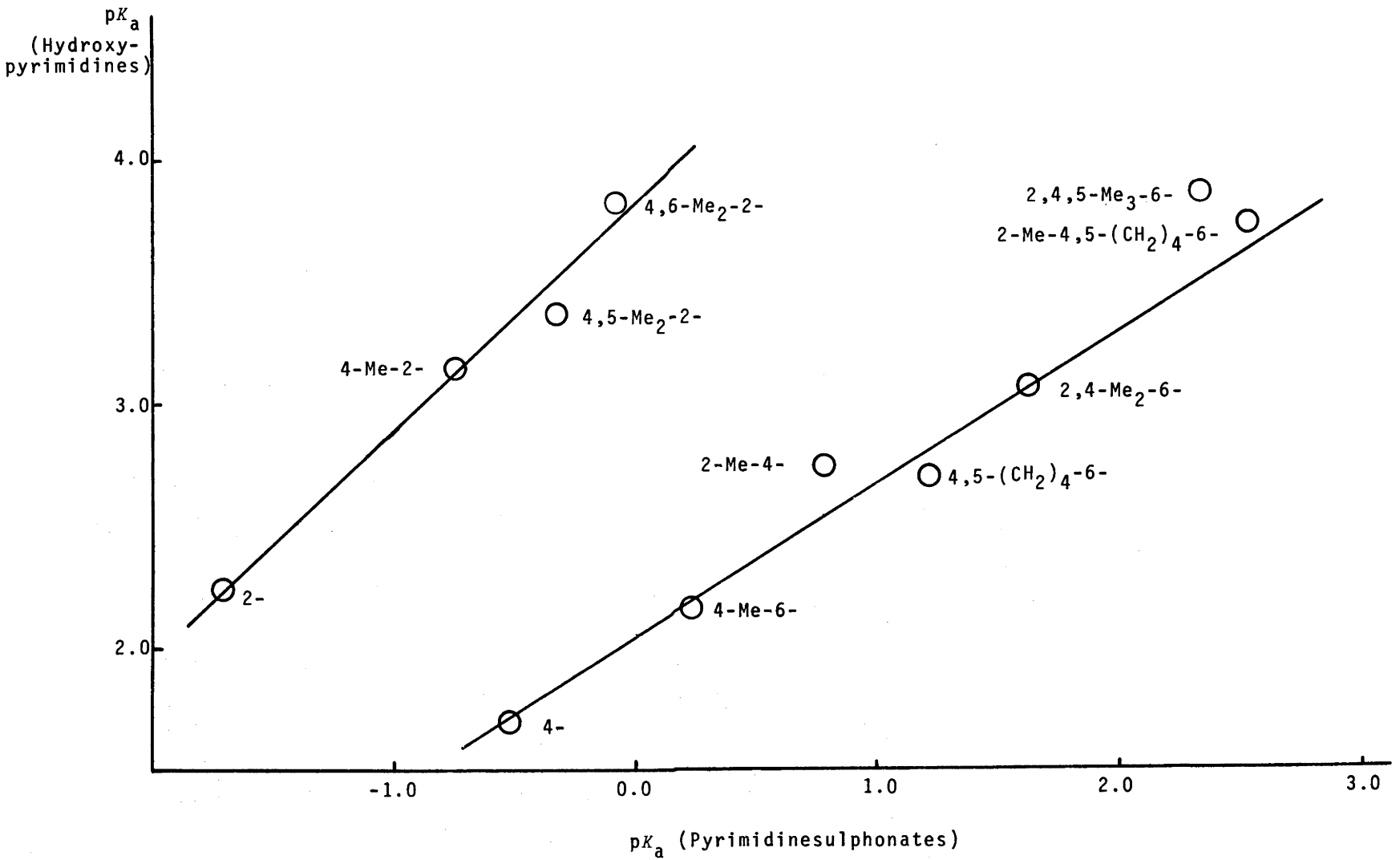
With one exception, rates of hydrolysis of the three heterocyclic systems studied were of the same order of magnitude. The extremely facile hydrolysis of potassium quinazoline-4-sulphonate was parallel to nucleophilic displacement reactions of other 4-substituted-quinazolines [*e.g.* 4-chloroquinazoline reacts with piperidine 10,000 times faster than its 2-isomer and *ca* 2000 times faster than 4-chloropyrimidine (Illuminati, 1964; Shepherd and Fedrick (1965)].

No linear free energy relationships between log(reaction rate) and the corresponding dissociation constants could be found. This supports the views of Jaffé (1953) that "since the Hammett equation does not apply to substituents in the *ortho* position, it appears questionable whether it can be applied to positions in heterocyclic compounds in which the side-chain is vicinal to a hetero-atom." However two linear free

energy relationships were found (3.4). Plots of the dissociation constants of pyrimidinesulphonates against the dissociation constants of the corresponding hydroxy compounds gave points close to straight lines for both the 2- and 4-compounds. The only major deviations occurred with fully (*C*-)substituted compounds in the 4-sulphonate series and, in retrospect, these might have been predicted (these two points were not included when calculating the linear regression line). Such plots have a predictive value: both the unknown potassium 4,5,6-trimethylpyrimidine-2-sulphonate and 5-methylpyrimidine-4-sulphonate would be expected to have a pK_a of about zero, and 5-methylpyrimidin-2-one should have a pK_a *ca* 2.7.

In conjunction with the above study the rates of reaction of the four pyrimidine-2-sulphonyl fluorides with methanolic sodium methoxide were measured (Table 3.4). The results were broadly parallel to those observed with the pyrimidine-2-sulphonates above (Table 3.2): a 4- or 6-methyl group decreased the reaction rate 3-4 fold and a 5-methyl group about 12 fold. The overall rates of reaction were approximately 200 times faster than the corresponding aqueous alkaline hydrolyses at the same temperature.

3.4


pKa (Hydroxy-pyrimidines)
4.0
3.0
2.0
-1.0
0.0
1.0
2.0
3.0
pKa (Pyrimidinesulphonates)
4,6-Me2-2-
4,5-Me2-2-
4-Me-2-
2-
2,4,5-Me3-6-
2-Me-4,5-(CH2)4-6-
2,4-Me2-6-
2-Me-4-
4,5-(CH2)4-6-
4-Me-6-
4-

CHAPTER 4

SPECTRA

A) Introduction

In this chapter, spectral properties of the compounds studied are tabulated and briefly discussed. With the exception of some compounds discussed in the section (E) on mass spectrometry, the compounds listed are those containing a sulphonyl group ($-SO_2-$). Practical details are given in the experimental chapter (5). Where relevant to the rate studies, some aspects of the u.v. spectra and dissociation constants have been discussed already in chapter 3.

B) Infra Red Spectroscopy

The i.r. spectra of sulphonic acids and their salts have not been investigated widely. However it is clear (Bellamy, 1958 and 1968) that vibrations of the sulphonate group are manifest in two regions, 1230-1120 and 1080-1025 cm^{-1}; in particular, aromatic sulphonates (Colthup *et al.*, 1964) often have bands at or near 1230, 1190, 1130 and 1040 cm^{-1}, representing the interaction of three SO and one SC vibrations. In the zwitterionic pyridine-2-sulphonic acid (Evans and H.C. Brown, 1962) bands appear at closely similar frequencies (Table 4.B.1) but the spectra of the pyrimidine-, purine-, and quinazoline-sulphonates are less simple: each shows a strong, broad, and complex band at 1255-1190 cm^{-1} in which up to three small partially resolved peaks may be

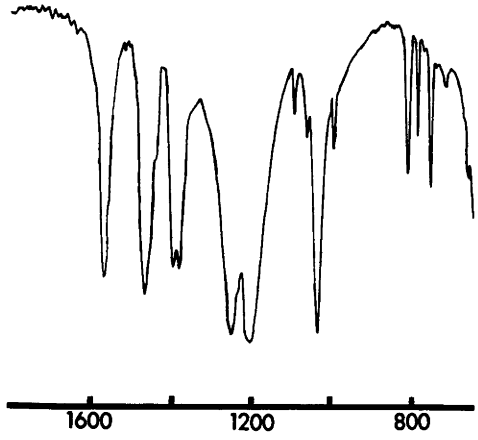
visible (region A) and a strong sharp band at 1070-1015 cm^{-1} (region B) (Table 4.B.1 and spectra on p.54A).

A number of bands have been associated with vibrations of the fluorosulphonyl group. The S-F stretching frequency, found at 779 cm^{-1} in benzenesulphonyl fluoride (Ham *et al.*, 1960) and 813 cm^{-1} in purine-6-sulphonyl fluoride (Beaman and Robins, 1961) is said to be characteristic of the group (Beaman and Robins, 1961). Bands due to the symmetric and antisymmetric $-SO_2-$ stretching frequencies are found in the regions 1185-1250 cm^{-1} and 1400-1450 cm^{-1} respectively (Detoni and Hadzi, 1957; Beaman and Robins, 1961). The positions of the strongest bands in the spectra of the five sulphonyl fluorides examined are in agreement with the above figures (Table 4.B.2 and spectra on p. 54B). Surprisingly the S-F stretching frequencies are closer to the value reported for benzenesulphonyl fluoride than that for purine-6-sulphonyl fluoride.

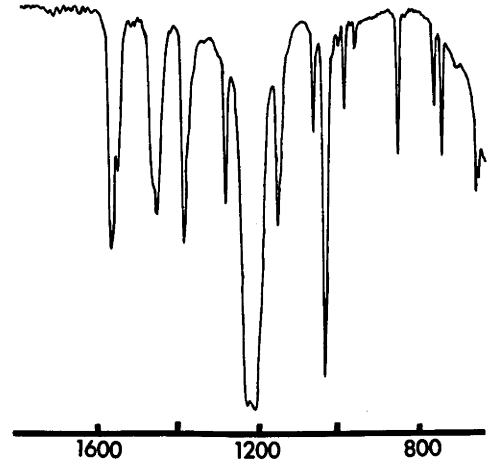
The $-SO_2-$ symmetric and antisymmetric vibrations are found at lower frequencies in the sulphonamides than in the sulphonyl fluorides (*cf.* Tables 4.B.2 and 4.B.3). Reported spectral regions for these vibrations are 1180-1140 cm^{-1} (s) and 1380-1310 cm^{-1} (as) (Colthup *et al.*, 1964). The region for symmetric vibration is extended to 1185 cm^{-1} in the present study. An anomaly was found in the spectrum of 2-(*NN*-di-isopropylsulphamoyl) -4,6-dimethylpyrimidine which has an intense band at 1235 cm^{-1}, the only strong band between 1450 and 1200 cm^{-1}.

I.r. Spectra of Sulphonates

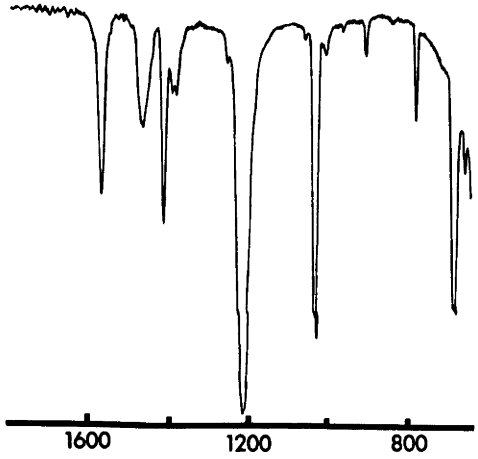
(Nujol mulls)



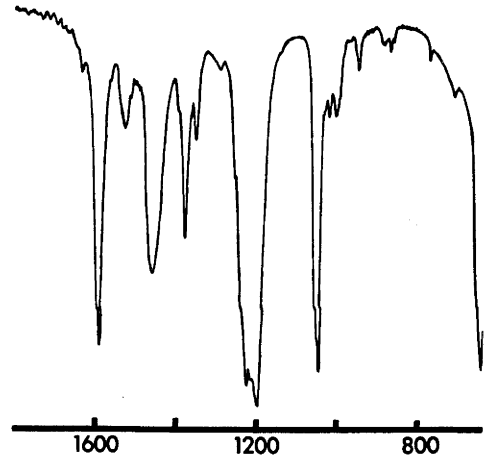
Pyrimidine-2-SO_3K



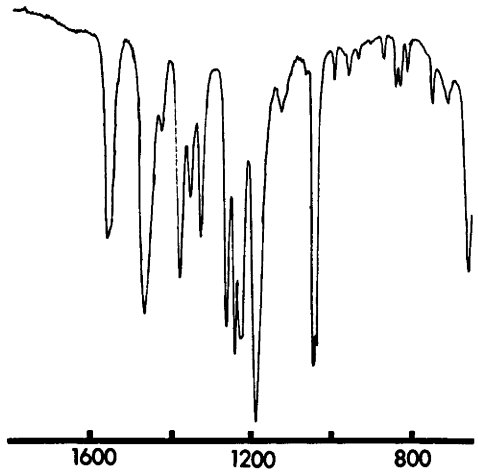
Pyrimidine-4-SO_3K



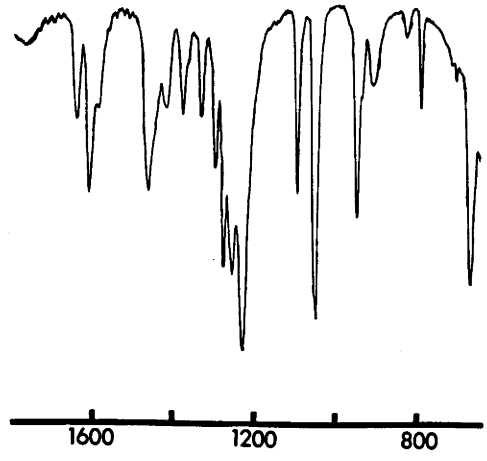
5-Me-pyrimidine-2-SO_3K



4,6-Me_2-pyrimidine-2-SO_3K



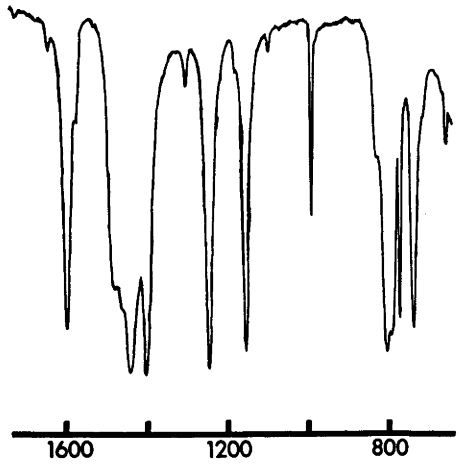
H_4-Quinazoline-4-SO_3K



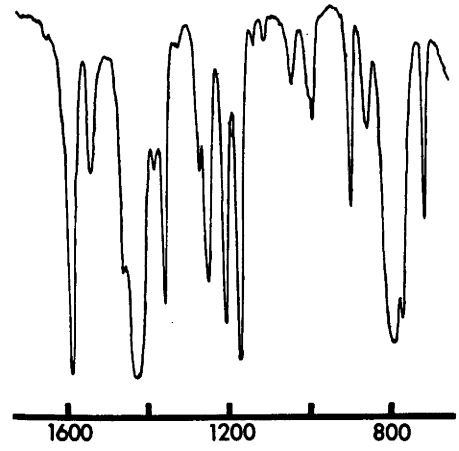
Purine-8-SO_3K,H_2O

I.r. Spectra of Sulphonyl Fluorides

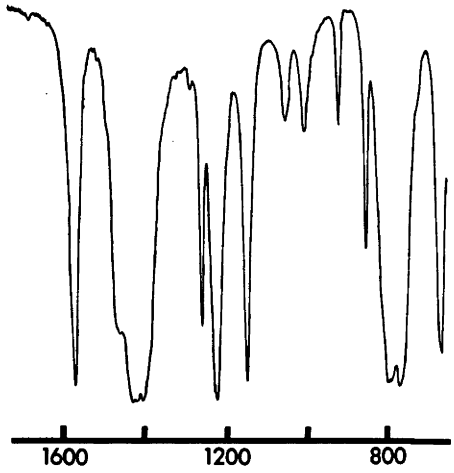
(Nujol mulls)



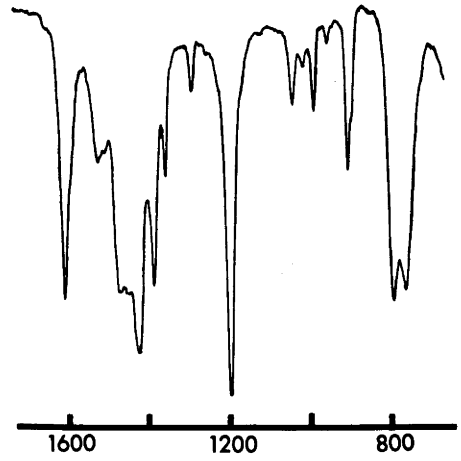
Pyrimidine-2-SO_2F



4-Me-pyrimidine-2-SO_2F



5-Me-pyrimidine-2-SO_2F



4,6-Me_2-pyrimidine-2-SO_2F

Table 4.B.1

Characteristic i.r. bands of sulphonates

Compound	Region A (cm^{-1})	Region B
Pyridine-2-SO_3H	1237, 1198, 1138	1032
Pyrimidine-2-SO_3K	1250, 1200	1032
4-Me	1251, 1232, 1203	1048
5-Me	1215	1034
4,5-Me_2	1245, 1220	1052
4,6-Me_2	1244, 1214	1062
Pyrimidine-6-SO_3K	1230, 1215	1044
2-Me	1255, 1198	1045
4-Me	1215	1048
2,4-Me_2	1254, 1232, 1210	1068
4,5-Me_2	1250, 1238, 1202	1029
2,4,5-Me_3	1202	(1055,1030,1015)[a]

Table 4.B.1 cont.

Purine-6-SO_3K	1235, 1190	1050
9-Me	1225	1048
Purine-8-SO_3K	1235	1050
H_4-Quinazoline-4-SO_3K	1245, 1230, 1195	(1045, 1040)[a]
2-Me	1240, 1210	1050
Quinazoline-2-SO_3K[b]	1235, 1200	1038
Quinazoline-4-SO_3K	1240, 1200	1055

[a] Partially resolved.

[b] See exptl. details in Chap.5.

Table 4.B.2

Characteristic i.r. bands of sulphonyl fluorides

Compound	SO_2 stretch (as) cm^{-1}	SO_2 stretch (s)	S-F stretch
Pyrimidine-2-SO_2F	(1440, 1400)[a]	1250	802, 790 [c]
4-Me	1425	1204	788
5-Me	(1426,1418,1400)[b]	1220	795, 788 [c]
4,6-Me_2	1422	1195	792
Quinazoline-2-SO_2F	1426	1232	790

[a] Peaks are of equal intensity and may arise from Fermi resonance between ν_{SO_2} (as) and another vibration, av. 1420 cm^{-1} (*cf.* Beaman and Robins, 1961).

[b] Partially resolved, and see note a.

[c] Definite assignment not possible.

Table 4.B.3

Characteristic i.r. bands of sulphonamides

Compound	SO_2 stretch (as), cm^{-1}	SO_2 stretch (s)
Pyrimidine-2-SO_2NH_2	1365	1150
4-Me	1358	1185
5-Me	1335	1185
4,6-Dimethylpyrimidine-		
2-SO_2NH_2	1355	1158
2-SO_2NEt_2	1350	1170
2-$SO_2NPr^i_2$	1235[a]	1185
2-$SO_2N(CH_2.CH_2)O$	1352	1150
2-$SO_2NH.NH_2$	1344	1162
2-$SO_2NH.N{:}CMe_2$	1340	1160
Purine-6-$SO_2NH.NH_2$	1358	1158

[a] Tentative assignment, see text.

If this band is correctly assigned to assymmetric stretching its very low frequency may be attributed to the effect of the extremely bulky di-isopropylamino group.

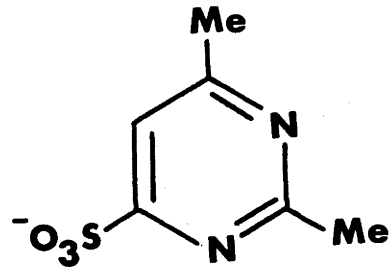
C) Ultra Violet Spectroscopy

The u.v. spectra of compounds not containing a sulphonyl group are recorded in the experimental chapter (5).

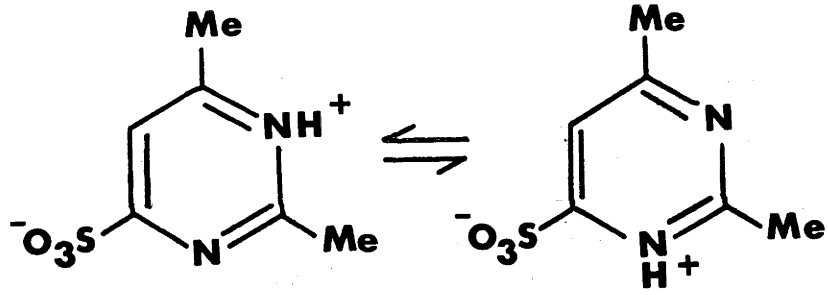
Spectra of compounds containing a sulphonyl group (Tables 4.C.1 and 4.C.2) were found to be simple, consisting generally of a single intense K-band. In the pyrimidinesulphonyl fluorides this band lies at a shorter wavelength than in the other compounds and here other longer wavelength bands were observed; these bands are presumably submerged in the sulphonamides and sulphonates. As expected (Mason, 1962), the K-band undergoes a bathochromic shift on substitution accompanied by an increase in intensity at $\lambda_{max.}$. The 2-substituted quinazolines have unusually intense K-bands, more intense than any recorded in a recent compilation of quinazoline spectra (Armarego, 1971) and comparable with those of naphthalene [221(4.98): Schindlbauer and Hagen, 1965] and 2-sulphonaphthalene [225(4.9): Horyna, 1962].

The spectra of the sulphonates (Table 4.C.2) must be considered together with their dissociation constants.

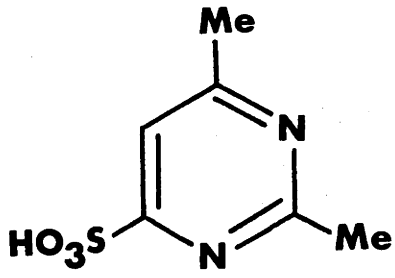
Within an H_0 range limited by the progressive instability of the sulphonic acids and by the rapid-reaction apparatus itself, only one pK_a emerged from each acid (with the exception of the purines: see below) using the spectrometric method. Clearly each such value represented the addition of a proton to the sulphonate anion, *e.g.* (4.1), to give the zwitterion (4.2) rather than the neutral species (4.3) because the change was accompanied by a small bathochromic shift and an increase in absorption at $\lambda_{max.}$ (Table 4.C.2), such phenomena are typical of *N*-protonation of the pyrimidine ring (Mason, 1962) and parallel to the behaviour of pyridinesulphonic acids (Evans and H.C. Brown, 1962 b). Moreover, had protonation occurred at the sulphonate group little, if any, spectral change would be expected, a postulate confirmed by the lack of appreciable change (G.R. Heys, personal communication) in the spectrum of toluenesulphonic acid [pK_a -1.1 (Bonner and Torres, 1965) or -1.3 (Dinius and Choppin, 1962); *cf.* methanesulphonic acid: -1.2 (Covington and Lilley, 1967)] from pH 7 to H_0 -5; likewise, any further protonation, *e.g.* (4.2) → (4.4), should be spectrally invisible. In the three purines examined the single pK_a for the 9-methyl compound clearly shows that the higher dissociation constants of 6- and 8-sulphopurine arise from loss of the proton on N-7/9. Where a sulpho group is situated between two nitrogen atoms there is an


Me
N
$^{-}O_3S$
N
Me

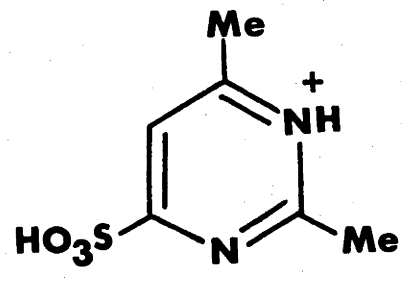
4.1


Me
NH+
$^{-}O_3S$
N
Me
Me
N
$^{-}O_3S$
N
H+
Me

4.2


Me
N
HO_3S
N
Me

4.3


Me
+
NH
HO_3S
N
Me

4.4

increase in the acid strength of the compound. 6-Sulphopurine and the 4-sulphopyrimidines have dissociation constants comparable with those of the parent compounds.

The pK_a values of the sulphopyrimidines (including the reduced quinazolines) (Table 4.C.2) indicate an appreciable increase with each added *C*-methyl group although the extent depends on position: ΔpK_a is 1.1 - 1.4 (2-Me), 0.7 - 1.0 (4- or 6-Me), and 0.4 - 1.0 (5-Me; but see below). Such positional dependence is seen in terms of the two ways (Evans and H.C. Brown, 1962 b; H.C. Brown and Mihm, 1955; Huheey, 1971) [inductive (+I) and hyperconjugative (+M)] in which a methyl group can affect the ease of protonation at each ring-nitrogen atom. Thus a 2-methyl group has a double effect on both these potential sites for protonation; a 4-methyl group has a double effect on one site but only a single effect on the other; and a 5-methyl group has only a single diminished (inductive) effect on both sites. In addition there is the possibility that steric interference may affect the pK_a. Where the presence of a 5-methyl group produces little or no steric interference the ΔpK_a is 0.4 - 0.5; but where there are three vicinal groups, as in potassium 4,5-dimethyl- and 2,4,5-trimethylpyrimidinesulphonate, it is doubled (0.7 - 1.0). The buttressing that will occur with three sterically large vicinal groups may

inhibit the approach of a proton to a ring nitrogen and so produce the unusually large decrease in acid strength observed (*cf.* Dippy and Hughes, 1963).

D) Proton Magnetic Resonance Spectroscopy

H^1 n.m.r. spectroscopy was used to confirm the structures of most of the compounds prepared (Table 4.D.1). Some difficulties were encountered due to the low solubilities of several purines and quinazolines: surprisingly no satisfactory spectrum could be obtained for potassium purine-6-sulphonate in D_2O in spite of an apparently sufficient solubility.

An early study was made of the acid hydrolysis of certain sulphonates (3.1 and p. 38) and this was used to confirm the structures of the hydrolytic products. The method was found to be less convenient than the u.v. spectroscopic method finally used (see Chapter 3).

Table 4.C.1

U.v. spectra of sulphonyl fluorides and sulphonamides

Compound[a]	$\lambda_{max.}$ (log ε)
Pyrimidine-	
2-SO_2F	238 (3.18), 243 (3.19), 248 (3.05)
2-SO_2F-4-Me	245 (3.33), 247 (3.33), 252 (3.22)
2-SO_2F-5-Me	243 (3.39), 248 (3.37), 256 (3.24)
2-SO_2F-4,6-Me_2	245 (3.38), 253 (3.25)
2-SO_2NH_2-4,6-Me_2[b]	248 (3.52)
2-SO_2NEt_2-4,6-Me_2	247 (3.67)
2-$SO_2NPr^i_2$-4,6-Me_2	248 (3.45)
2-$SO_2N(CH_2CH_2)_2O$-4,6-Me_2	246 (3.64)
2-SO_2NHNH_2-4,6-Me_2	247 (3.45)
Purine-	
6-SO_2NHNH_2	276 (3.98), 330 (3.01)
Quinazoline-	
2-SO_2F	231 (4.99), 277 (3.40), 280 (3.40) 299 (3.36), 314sh. (3.25)

[a] In methanol.

[b] In water.

Table 4.C.2

Ionization and u.v. spectra of the sulphonic acids

Compound[a]	pK_a [b] (Anal. λ)	$\lambda_{max.}$ (log ε)
Pyrimidine-		
2-SO_3K	-1.70±0.07 (250)	243.5(3.30), 246(3.33)
4-Me-2-SO_3K	-0.76±0.07 (252)	248(3.43)
5-Me-2-SO_3K	-1.21±0.06 (265)	253(3.43)
4,5-Me_2-2-SO_3K	-0.33±0.04 (265)	253(3.56)
4,6-Me_2-2-SO_3K	-0.09±0.04 (255)	248(3.50)
4-SO_3K	-0.53±0.02 (255)	245.5(3.60),250.5(3.65), 256(3.51)
2-Me-4-SO_3K	0.78±0.04 (260)	256(3.71), 262(3.60)
4-Me-6-SO_3K	0.23±0.04 (262)	252(3.65)
2,4-Me_2-6-SO_3K	1.62±0.04 (270)[c]	257(3.55); 263(3.56)[d]
4,5-Me_2-6-SO_3K	1.20±0.04 (275)[c]	260(3.74); 266(3.88)[d]
2,4,5-Me_3-6-SO_3K	2.33±0.04 (276)[c]	264(3.72); 269(3.84)[d]
Purine-		
6-SO_3K	1.13±0.05 (285)	275(3.93)[i]
	8.56±0.05 [e,f]	
9-Me-6-SO_3K	1.14±0.06 (290)	274(3.99)[j]
8-SO_3K	2.22±0.04 (270)	269(4.10)[k],277.5(4.11)[l]
	6.93±0.02 (280)[c,f]	

Table 4.C.2 contd.

Quinazoline-			
2-SO_3K [g]	0.25±0.04	(273)	231(4.90), 272(3.49), 299.5(3.35)[j]
4-SO_3K	—— [h]		232(4.55), 315(3.60)[j]
5,6,7,8-H_4-4-SO_3K	1.21±0.04	(280)	264(3.78)[j]
5,6,7,8-H_4-2-Me-4-SO_3K	2.52±0.02	(286)[c]	270(3.79)

---

a Spectra measured in aqueous solution; where necessary, allowance made for associated potassium chloride in recording log ε.

b Addition of proton to nitrogen atom of anion at 25°; determinations carried out using a rapid-reaction technique.

c At 20°; rapid-reaction technique not used.

d Zwitterion at H_0 -1.

e Value of Doerr *et al.*, 1961.

f Loss of a proton from N-7/9.

g Crude material: log ε values tentative and based on the assumption that material was anhydrous.

h Too unstable for measurement.

i In buffer of pH 6.

j In buffer of pH 7.

k In buffer of pH 4.

l In buffer of pH 10.

Table 4.D.1

H^1 n.m.r. spectra of heterocyclic compounds [a]

Compound [b]		δ [c]
1) Hydroxy and Chloro compounds:		
Pyrimidines		
4-OH-2-Me	(A)	Me: 2.64; 5-H: 6.64 (d, *J* 7); 6-H: 8.17 (d, *J* 7)
4-OH-6-Me	(B)	Me: 2.48 (d, *J* 1); 5-H: 6.66 (m)[e]; 2-H: 9.28 (m)[e]
2-OH-4,5-Me_2	(B)	5-Me: 2.24; 4-Me: 2.69[f]; 6-H: 8.54
2-OH-4,6-Me_2	(B)	4-Me and 6-Me: 2.64; 5-H: 6.85
4-OH-2,6-Me_2	(A)	6-Me: 2.26; 2-Me: 2.42; 5-H: 6.20
	(B)[d]	6-Me: 2.44; 2-Me: 2.74[f]; 5-H: 6.53
4-OH-5,6-Me_2	(B)	5-Me: 2.13; 6-Me: 2.51; 2-H: 9.23
4-Cl-6-OH-5-Me	(D)	Me: 2.21; 2-H: 8.13
2-Cl-4-Me	(E)	Me: 2.50; 5-H: 7.11 (d, *J* 5.5); 6-H: 8.47 (d, *J* 5.5)
2-Cl-5-Me	(E)	Me: 2.32; 4-H and 6-H: 8.38
2-Cl-4,5-Me_2	(F)	5-Me: 2.32; 4-Me: 2.47; 6-H: 8.41
4-Cl-2-Me	(D)	Me: 2.78; 5-H: 7.35 (d, *J* 4); 6-H: 8.76 (d, *J* 4)
4-Cl-2,5,6-Me_3	(E)	5-Me: 2.29; 6-Me: 2.44; 2-Me: 2.55
2,4-Cl_2-6-Me	(E)	Me: 2.50; 5-H: 7.20
2,4,6-Cl_3-5-Me	(E)	Me: 2.50

Table 4.D.1 contd. page 2

5,6,7,8-H_4-Quinazolines

4-OH	(A)	Cyclohexene ring: 1.73 (m)[e] and 2.47 (m)[e]; 2-H: 8.11
4-OH-2-Me,HCl	(A)	Cyclohexene ring: 1.79 (m)[e] and 2.45 (m)[e,h]; Me: 2.61

2) Mercapto and related compounds:

Pyrimidines

2-SNH_2-4,6-Me_2	(G)	4-Me and 6-Me: 2.39; NH_2: 3.96 (br); 5-H: 6.95
2-SH-4-Me	(G)	4-Me: 2.30; 5-H: 6.77 (d, J 6); 6-H: 8.15 (d, J 6)
2-SH-5-Me	(G)	5-Me: 2.07; 4-H and 6-H: 8.20
2-SH-4,6-Me_2	(G)	4-Me and 6-Me: 2.29; 5-H: 6.68
2-S.S-2'	(G)	5-H: 7.41 (t, J 5); 4-H and 6-H: 8.78 (d, J 5)
4,4'-Me_2-2-S.S-2'	(G)	4-Me: 2.39; 5-H: 7.25 (d, J 5) 6-H: 8.61 (d, J 5)
5,5'-Me_2-2-S.S-2'	(G)	5-Me: 2.19; 4-H and 6-H: 8.61
4,4',6,6'-Me_4-2-S.S-2'	(G)	4-Me and 6-Me: 2.35; 5-H: 7.11
	(D)	4-Me and 6-Me: 2.39; 5-H: 6.81

Purines [i]

2-SH	(G)	8.39; 8.52
6-SH	(G)	8.23; 8.42
8-SH	(G)	8.46; 8.68

Table 4.D.1 contd. page 3

Pyrazolo[3,4-*d*]pyrimidines

3-NH_2-4-CN-pyrazole [j]	(G)	NH_2: 5.95 (br); 5-H: 7.68
4-SH [i]	(G)	8.08; 8.21
4-SMe	(G)	Me: 2.71; 8.24[i]; 8.71[i]

5,6,7,8-H_4-Quinazolines

4-SH	(G)	Cyclohexene ring: 1.62 (m)[e] and 2.42 (m)[e]; 2-H: 8.11
4-SH-2-Me	(G)	Cyclohexene ring: 1.67 (m)[e] and 2.50 (m)[e]; Me: 2.33

3) Sulphonates:

Pyrimidines

2-SO_3K	(A)	5-H: 7.76 (t, J 6); 4-H and 6-H: 9.13 (d, J 6)
4-Me-2-SO_3K	(A)	Me: 2.61; 5-H: 7.61 (d, J 5.1); 6-H: 8.82 (d, J 5.1)
5-Me-2-SO_3K	(A)	Me: 2.36; 4-H and 6-H: 8.77
4,5-Me_2-2-SO_3K	(A)	5-Me: 2.34; 4-Me: 2.56; 6-H: 8.58
4,6-Me_2-2-SO_3K	(A)	4-Me and 6-Me: 2.54; 5-H: 7.45
4-SO_3K	(A)	5-H: 8.11 (q, $J_{4,5}$ 5, $J_{2,5}$ 1); 6-H: 9.21 (d, $J_{4,5}$ 5); 2-H: 9.41 (br)
2-Me-4-SO_3K	(A)	Me: 2.82; 5-H: 7.99 (d, J 6); 6-H: 9.16 (d, J 6)

Table 4.D.1 contd. page 4

4-Me-6-SO_3K	(A)	Me: 2.65; 5-H: 7.94 (d, J 1); 2-H: 9.18 (d, J 1)
2,4-Me_2-6-SO_3K	(A)	4-Me: 2.64; 2-Me: 2.75; 5-H: 7.76
	(B)[d]	4-Me: 2.83; 2-Me: 2.92; 5-H: 8.17
4,5-Me_2-6-SO_3K	(A)	4-Me and 6-Me: 2.58; 2-H: 8.94
	(B)[d]	5-Me: 2.73; 4-Me: 2.91; 2-H: 9.42
2,4,5-Me_3-6-SO_3K	(A)	4-Me and 5-Me: 2.53; 2-Me: 2.65

Purines

8-SO_3K[i]	(A)	8.96; 9.15
9-Me-6-SO_3K	(A)	Me: 1.95; 8.57[i]; 8.98[i]

Quinazolines

4-SO_3K	(A)	Benzene ring: 8.72 (m); 2-H: 9.30
5,6,7,8-H_4-4-SO_3K	(A)	Cyclohexene ring: 1.86 (m)[e] and 3.04 (m)[e]; 2-H: 8.88
5,6,7,8-H_4-2-Me-4-SO_3K	(A)	Cyclohexene ring: 1.84 (m)[e] and 2.93 (m)[e]; 2-Me: 2.61

4) Sulphonyl Fluorides:

Pyrimidines

2-SO_2F	(D)	5-H: 7.85 (t, J 5); 4-H and 6-H: 9.20 (d, J 5)

Table 4.D.1 contd. page 5

4-Me-2-SO_2F	(D)	4-Me: 2.76; 5-H: 7.78 (d, *J* 5); 6-H: 8.99 (d, *J* 5)
5-Me-2-SO_2F	(D)	5-Me: 2.60; 4-H and 6-H: 8.99
4,6-Me_2-2-SO_2F	(G)	4-Me and 6-Me: 2.61; 5-H: 7.85
Purine		
6-SO_2F [i]	(G)	9.08; 9.26
Quinazoline		
2-SO_2F	(D)	Benzene ring: 8.14 (m); 4-H: 9.60

5) Sulphonamides:

Pyrimidines		
4-Me-2-SO_2NH_2	(A)	4-Me: 2.80; 5-H: 7.87 (d, *J* 6); 6-H: 9.05 (d, *J* 6)
4,6-Me_2-2-SO_2NH_2	(G)	4-Me and 6-Me: 2.54; 5-H: 7.53
4,6-Me_2-2-SO_2NHEt	(D)	Et: 1.20 (t, *J* 7), 3.35 (q, *J* 7); 4-Me and 6-Me: 2.60; NH: 4.96 (br t, *J* *ca* 6); 5-H: 7.25
4,6-Me_2-2-SO_2NEt_2	(D)	Et: 1.20 (t, *J* 7), 3.48 (q, *J* 7); 4-Me and 6-Me: 2.58; 5-H: 7.24
4,6-Me_2-2-$SO_2NPr^i{}_2$	(A)	^{i}Pr: 1.34 (d, *J* 6.3), 3.61 (m); 4-Me and 6-Me: 2.62; 5-H: 7.75
4,6-Me_2-2-SO_2NHNH_2	(D)	4-Me and 6-Me: 2.61; NH_2: *ca* 3.9 (br); 5-H: 7.28

Table 4.D.1 contd. page 6

4,6-Me_2-2-$SO_2NHN{:}CMe_2$	(D)	CMe_2: 1.93; 4-Me and 6-Me: 2.56; 5-H: 7.22

6) Amines and Azides:

Pyrimidines

2-$NHNH_2$-5-Me	(D)	5-Me: 2.21; NH_2: 4.0 (br); NH: 6.95 (br); 4-H and 6-H: 8.51
4-$NHNH_2$-2,6-Me_2	(A)	2-Me and 6-Me [i]: 2.27, 2.38; 5-H: 6.44
	(C)	2-Me and 6-Me [i]: 2.55, 2.71; 5-H: 6.98
2-N_3-5-Me	(G)[g]	5-Me: 2.55; 2-H and 4-H [i]: 9.37 (d, J 2), 9.94 (br d, J 2)
	(H)	5-Me: 2.65; 2-H and 4-H: 9.20

---

[a] Thiones and the corresponding oxo compounds are designated as mercapto and hydroxy compounds respectively for convenience.

[b] Solvents: A = D_2O, B = M-DCl in D_2O, C = 2 M-D_2SO_4 in D_2O, D = $CDCl_3$, E = CCl_4, F = no solvent, G = $(CD_3)_2SO$, H = $F_3C.COOH$.

[c] Singlet peaks unless indicated otherwise: J in Hz; Me_4Si or $Me_3Si(CH_2)_3SO_3Na$ as internal standard.

Table 4.D.1 contd. page 7

[d] Methyl assignments tentative.

[e] Poorly resolved.

[f] Slowly disappears by deuteriation; *cf.* T.J. Batterham, D.J. Brown and M.N. Paddon-Row, *J. Chem. Soc.* (B), 1967, 171.

[g] Present in this solvent as the tautomer 6-methyltetrazolo[1,5-*a*]pyrimidine; *cf.* Temple and Montgomery, 1965.

[h] Partly submerged beneath methyl peak.

[i] Peaks unassigned.

[j] Intermediate in the preparation of these compounds.

E) Mass Spectrometry

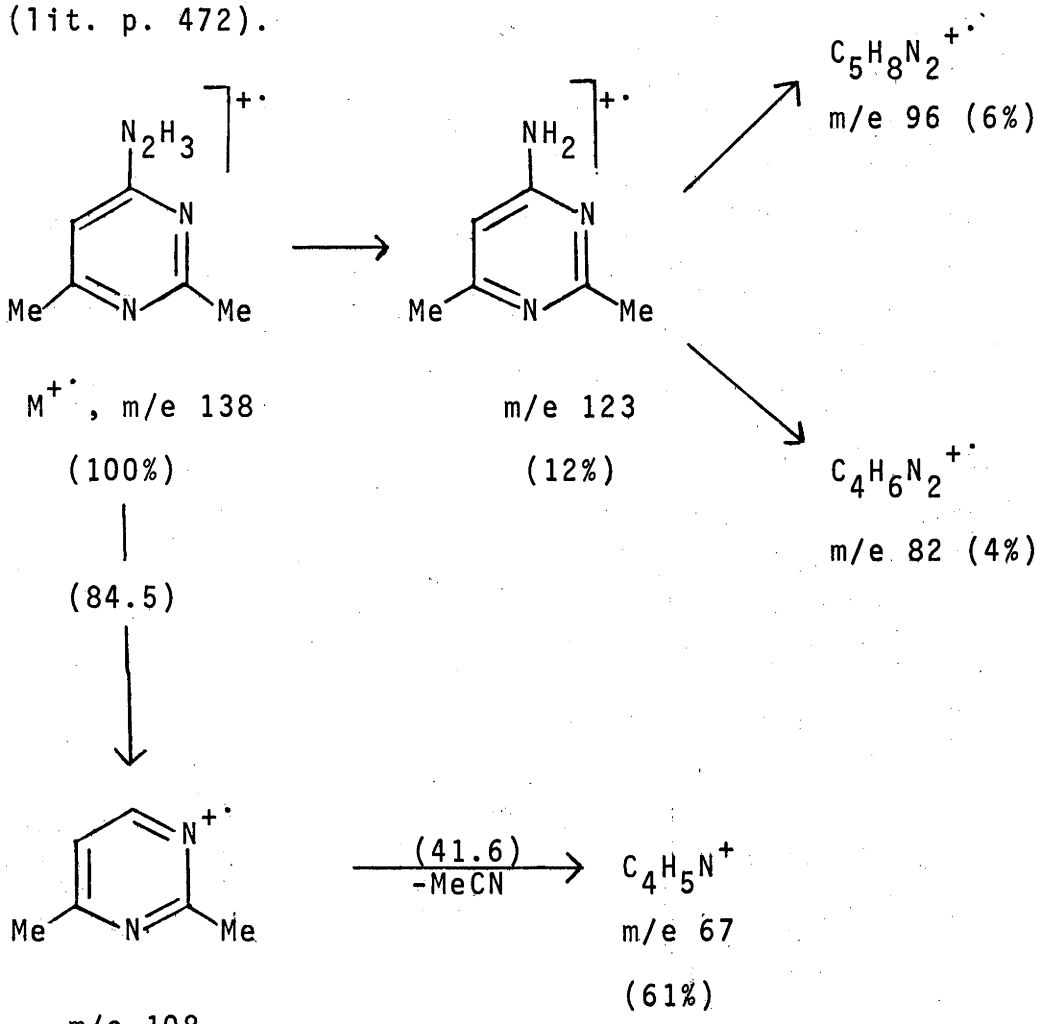
Mass spectrometry was used to prove the structure of *NN*'-bis(2,4-dimethylpyrimidin-6-yl)hydrazine. Also because elemental analysis could not distinguish between thiones (thiols) and their corresponding disulphides, the technique was used to confirm circumstantial evidence (physical properties, elemental analysis, and other spectra) for the structure of the latter compounds. The mass spectra of some other compounds were measured either for comparison with those of the compounds mentioned above, or to confirm suspected structures.

The abbreviation "lit." refers to the book by Porter and Baldas (1971) unless otherwise stated. Except where supported by the literature, all recorded breakdown patterns are speculative; where the presence of a metastable peak provides evidence for a transition this is given in parentheses between the two species. Generally the breakdown patterns are considered only as far as a species equivalent to the parent ring system; thereafter the patterns corresponded to those published. Additional data are given only when they highlight the relative importance of a particular pathway. Literature nomenclature is used.

(a) Substituted Hydrazines:

4-Hydrazino-2,6-dimethylpyrimidine

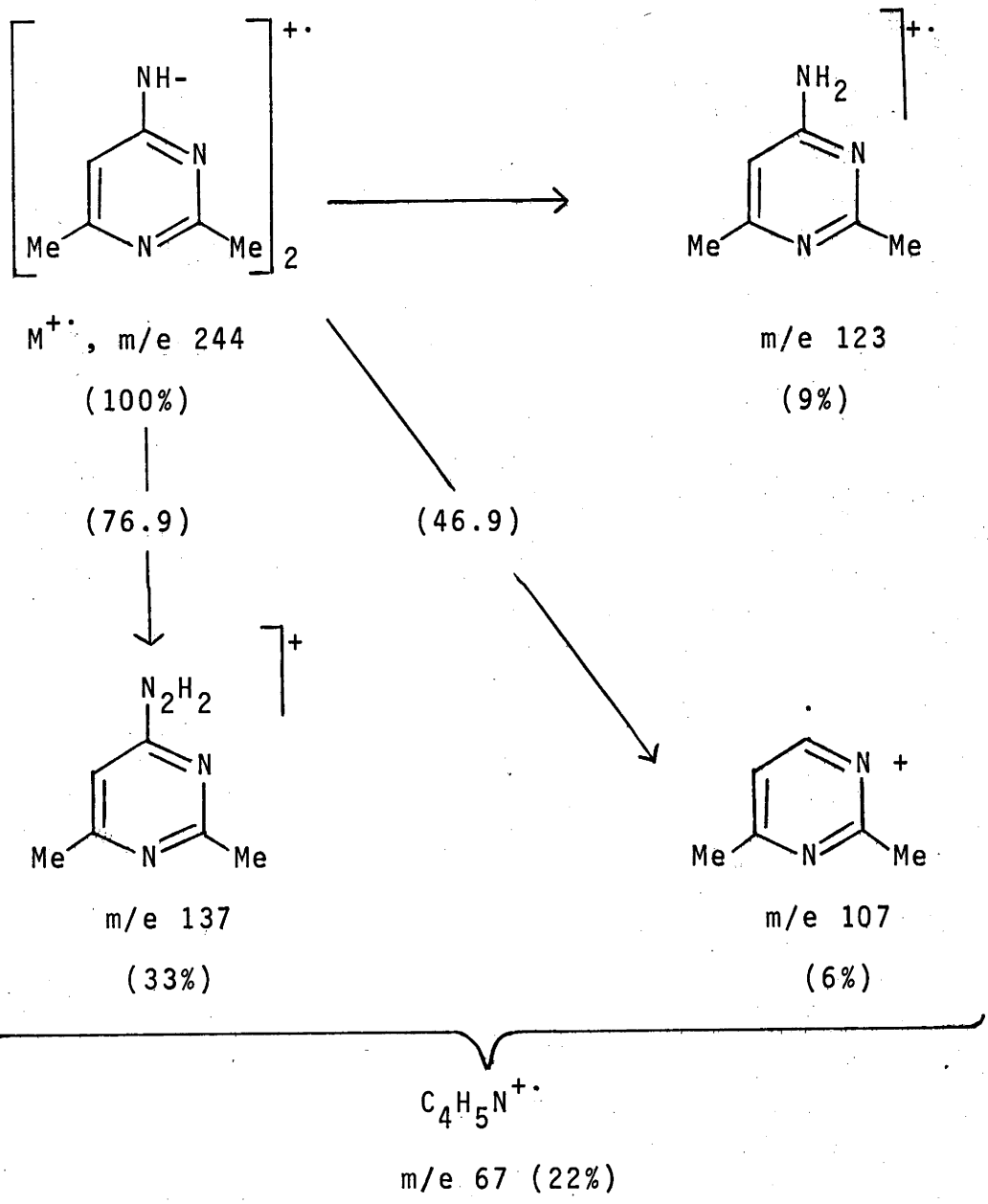
Either complete loss of the hydrazino radical occurred or there was rupture of the N-N bond to give a species derived from 4-amino-2,6-dimethylpyrimidine (lit. p. 472).



NN'-bis(2,4-dimethylpyrimidin-6-yl)hydrazine

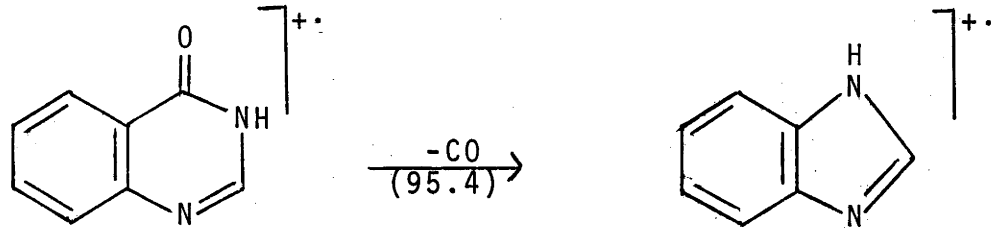
The hydrazine underwent a symmetric breakdown (rupture of the N-N bond), or an asymmetric breakdown (rupture of the C-N bond). High resolution mass spectrometry was used to obtain accurate m/e values for the molecular ion and two of the major fragments.

m/e measured	m/e expected	empirical formula
244.143716	244.143637	$C_{12}H_{16}N_6$
137.082614	137.082717	$C_6H_9N_4$
123.079505	123.079643	$C_6H_9N_3$



4-Hydrazinoquinazoline

The spectrum of a crude sample of this compound contained, in addition to the expected peaks, a set attributable to quinazolin-4-one (lit. p.481).



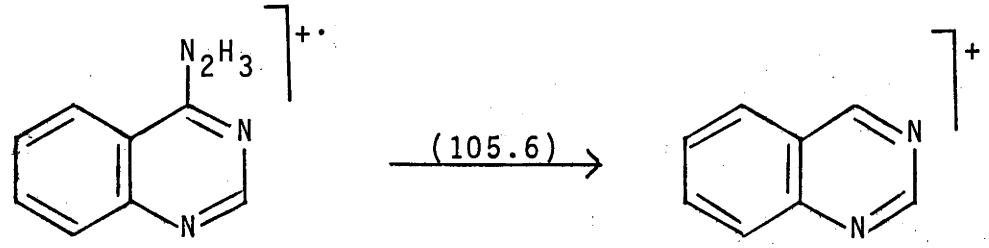
$M^{+\cdot}$, m/e 146 (100%)

m/e 118 (48%)

-HCN

m/e 91 (19%) ← -HCN — m/e 64 (16%)

4-Hydrazinoquinazoline first lost the hydrazino radical to give a quinazoline ion which successively lost two molecules of HCN (lit. p.480).



$M^{+\cdot}$, m/e 160 (100%)

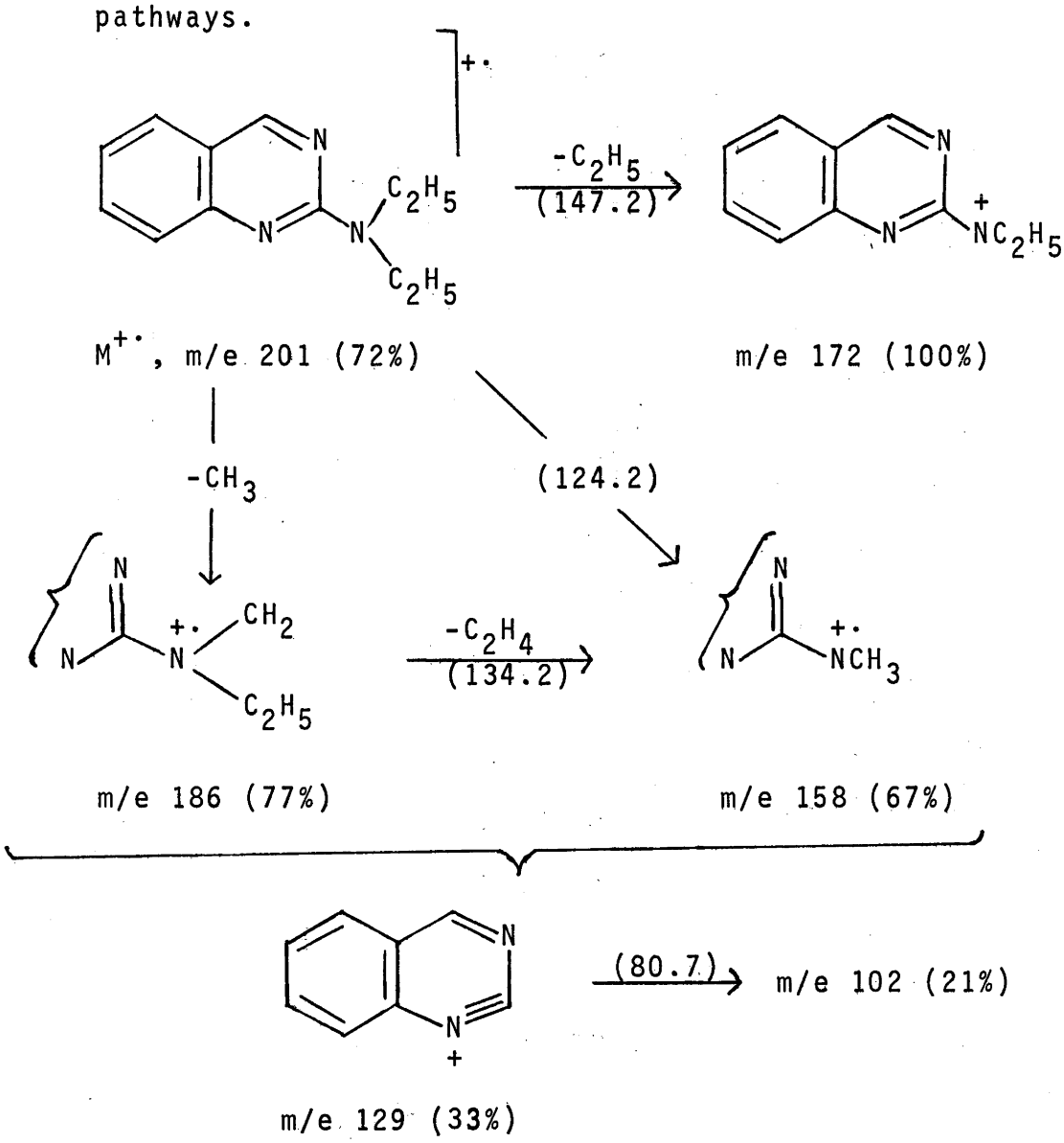
m/e 130 (38%)

-HCN

m/e 103 (39%) ← -HCN — m/e 76 (31%)

(b) 2-Diethylaminoquinazoline:

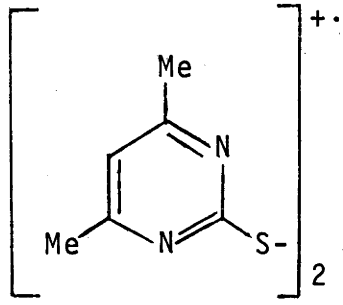
There was an initial complex breakdown of the side-chain with loss of C_2H_5, CH_3 and/or CH_2 fragments (see Budzikiewicz *et al.*, 1967, p.298) to give finally a quinazoline ion (lit. p.480). From the metastable peaks observed the breakdown apparently followed several pathways.



(c) Disulphides:

Bis(4,6-dimethylpyrimidin-2-yl) disulphide

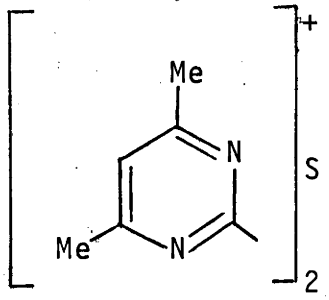
As with the other disulphides studied there was an initial loss of sulphur, first as a sulphydryl radical and then as elemental sulphur. Alternatively both sulphur atoms were expelled to form the equivalent of a bisdimethylpyrimidinyl ion [*cf.* Diphenyl disulphide: Budzikiewicz *et al.* (1967), p.293; Bowie *et al.*, 1969].



$\xrightarrow[(164.7)]{-S_2}$ Bis(4,6-dimethylpyrimidinyl)$^{+\cdot}$ m/e 214 (23%)

$M^{+\cdot}$, m/e 278 (100%)

$\xrightarrow[(215.9)]{-SH}$



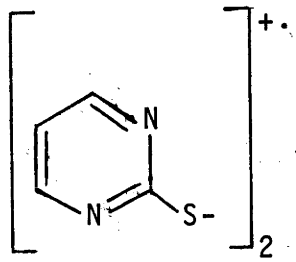
$\xrightarrow[(185.2)]{-S}$ Bis(4,6-dimethylpyrimidinyl)$^{+}$ m/e 213 (83%)

m/e 245 (30%)

Symmetrical cleavage of the bipyrimidinyl ion gave a fragment m/e 107 (26%) which lost MeCN and gave m/e 67 (48%) (*cf.* 4-hydrazino-2,6-dimethylpyrimidine).

Dipyrimidin-2-yl disulphide

In this compound loss of sulphur occurred only by the expulsion of both sulphur atoms together. The breakdown pattern of the resultant bipyrimidinyl ion included not only all the peaks found in the spectrum of authentic 2,2'-bipyrimidinyl (kindly supplied by Dr D.D. Bly, E.I. du Pont de Nemours, Wilmington) (see below) but also another set.



$\xrightarrow[(112.5)]{-S_2}$ Bipyrimidinyl $^{+\cdot}$ (A)

m/e 158 (100%)

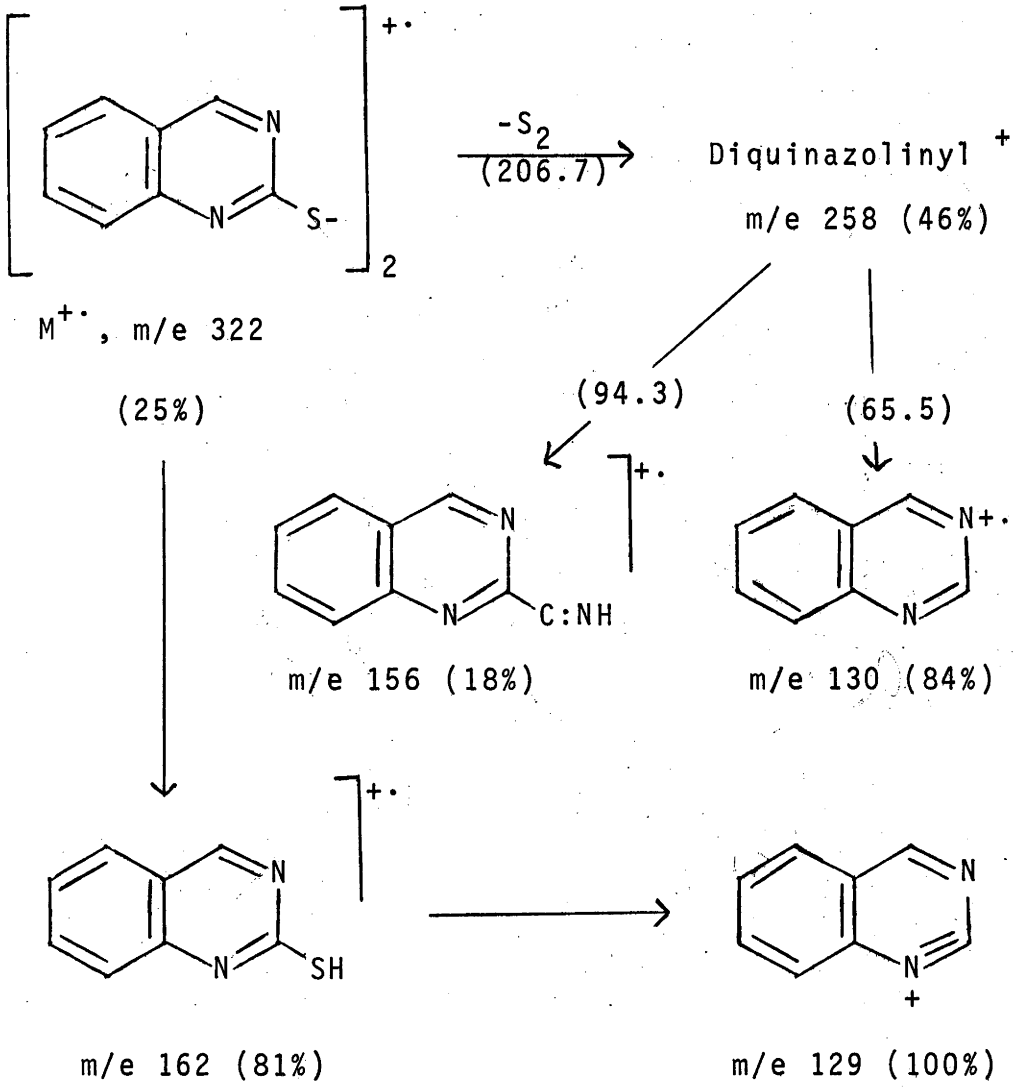
$M^{+\cdot}$, m/e 222 (92%)

	Intensities (%)	
m/e	(A)	(B)[a]
158	100	12
157	-	100
143	8	-
132	10	-
131	7	15
112	32	-
111	10	-
105	4	50
85	8	-
84	18	-
80	37	-
79	53	15

a 2,2'-Bipyrimidinyl.

Diquinazolin-2-yl disulphide

Expulsion of two atoms of sulphur occurred to give a biquinazolinyl ion. In addition, peaks corresponding to quinazoline-2-thione and its breakdown occurred; because of the ambiguity over which transitions give rise to the observed metastable peaks it was not possible to ascertain whether these resulted from symmetrical splitting of the disulphide (Budzikiewicz *et al.*, 1967, p.293) or from quinazoline-2-thione itself present as an impurity. Quinazoline-2-thione was shown not to contain the corresponding disulphide.



Metastable peaks were observed at m/e *ca* 80.5 and *ca* 81.5, possible transitions are:-

$$322 \xrightarrow{(80.5)} 161$$

$$129 \xrightarrow{(80.7)} 102$$

$$322 \xrightarrow{(81.5)} 162$$

$$130 \xrightarrow{(81.6)} 103$$

Comparison of the spectra of diquinazolin-2-yl disulphide (A) and quinazoline-2-thione (B).

	Intensities (%)	
m/e	(A)	(B)
322	25	-
258	46	-
162	81	100
156	18	-
134	35[a]	12
130	84	-
129	100	56
118	-	14
103	46	18
102	92	13

[a] From m/e 161 (metastable peak at 111.5).

CHAPTER 5

EXPERIMENTAL

EXPERIMENTAL

GENERAL

Microanalyses were carried out by Dr J.E. Fildes and her staff in the Department of Medical Chemistry, Australian National University, Canberra.

Melting points were taken in Pyrex capillaries and are uncorrected.

Thin layer chromatography was performed on silica-coated plates; spots were made visible by u.v. light and/or iodine vapour.

Infrared spectra were measured on Nujol mulls in a Unicam SP200 spectrophotometer. Ultraviolet spectra were generally measured using a Unicam SP800 spectrophotometer and the peaks were checked with a Unicam SP500 manual instrument. All work involving the stopped flow rapid reaction apparatus was carried out on a Shimadzu RS27 spectrophotometer. Where u.v. spectra are given in the body of the text, the wavelength of a maximum is given (in nm) followed by its intensity (log ε) in parenthesis. Inflexions and shoulders are underlined; in addition, shoulders are so marked. Ionisation constants were measured spectrophotometrically at concentrations below 10^{-3}M, where possible in buffers (Perrin, 1963) of 10^{-2}M ionic strength; thermodynamic corrections were not applied.

For unstable sulphonates of low pK_a, a stopped flow rapid reaction technique (Perrin, 1965) [if necessary, in conjunction with an extrapolation procedure (Albert and Serjeant, 1971) to avoid the exothermic dilution of concentrated acids] was used.

Mass spectrometry was used for the determination of molecular weights and the verification of structure. Spectra were recorded on a MS9 instrument by courtesy of Dr J.K. MacLeod, Research School of Chemistry.

^{1}H N.m.r. spectra were measured at 60 MHz and 33.5^o by Mr S.E. Brown, using tetramethylsilane or sodium 3-trimethylsilylpropane sulphonate as internal standard.

PYRIMIDINES

The following pyrimidinones were prepared according to the published methods indicated:-

(a) By direct synthesis:

4,6-Dimethylpyrimidin-2(1*H*)-one hydrochloride (used crude)(Kosolapoff and Roy, 1961).

2,4-Dimethylpyrimidin-6(1*H*)-one (used crude) (Pinner, 1889).

4,5-Dimethylpyrimidin-2(1*H*)-one hydrochloride (used crude)[pK_a (20°) 3.37±0.02 (anal.λ 317 nm)] (Sugasawa *et al.*, 1951; Albert and Reich, 1960).

4,5-Dimethylpyrimidin-6(1*H*)-one (used crude) [m.p. 200.5-202.5° (Hull *et al.*, 1946: m.p.202-204°)].

2,4,5-Trimethylpyrimidin-6(1*H*)-one hydrochloride [m.p. (EtOAc) 168° (Pinner, 1889: m.p. 168°); pK_a (20°): 3.86±0.04 (anal.λ 238 nm); and 10.24±0.04 (anal.λ 290 nm); u.v. absorption maxima (H_2O):-

pH 12.5 (anion): 266(3.85); 232(3.90),

pH 6.0 (neutral mol.): 259(3.90); 235(3.90);

pH 0.0 (cation): 238(4.07); 264sh(3.80)].

4,5,6-Trimethylpyrimidin-2-(1*H*)-one hydrochloride [pK_a (20°): 4.21±0.02 (anal. λ 320 nm) and 10.85±0.05 (anal. λ 310 nm)](Jones and Rees, 1969),

5-Methylbarbituric acid (after Vogel, 1956, p.1001 *et seq.*)[m.p.199-201° (Gerngross, 1905: m.p. 196°)].

(b) By indirect synthesis:

4-Methylpyrimidin-6(1*H*)-one (used crude)[from the reductive desulphurization of 6-methyl-2-thiouracil with Raney nickel (Marshall and Walker, 1951, modified after D.J. Brown, 1950)].

The above pyrimidinones (with the exception of 4,5,6-trimethylpyrimidin-2-one) were converted by phosphoryl chloride into the following chloro compounds:-

2-Chloro-4,6-dimethylpyrimidine [b.p. 163°/170 mmHg (Kosolapoff and Roy, 1961: b.p. 210-212°/760 mmHg, 118°/15 mmHg; m.p. 38-39°)].

4-Chloro-2,6-dimethylpyrimidine [b.p. 136-138°/180 mmHg (Schmidt, 1902: 81°/15 mmHg; Caton *et al.*, 1967: b.p. 182°)].

2-Chloro-4,5-dimethylpyrimidine [b.p. 160-164°/96 mmHg (Sugasawa *et al.*, 1951: m.p. 22.5-26°)].

4-Chloro-5,6-dimethylpyrimidine [sublimed 30°/0.6 mmHg (Hull *et al.*, 1946: b.p. 206°, m.p. 48°)].

4-Chloro-2,5,6-trimethylpyrimidine [b.p. 138°/85 mmHg (Hull *et al.*, 1946: b.p. 215°)].

2,4,6-Trichloro-5-methylpyrimidine [sublimed 100°/0.5 mmHg, m.p. 67-68° (Gerngross, 1905: b.p. 245.5°/748 mmHg, m.p. 67.5-68°)].

4-Chloro-6-methylpyrimidine [b.p. 107-108°/100 mmHg (Marshall and Walker, 1951: b.p. 65.5-66.5°/12 mmHg, m.p. 34.5-36°)].

2-Chloro-4-methylpyrimidine

2,4-Dichloro-6-methylpyrimidine, made by the action of phosphoryl chloride on 6-methyluracil (after Gabriel and Colman, 1899b), had b.p. 120°/28 mmHg (Marshall and Walker, 1951: b.p. 108°/18.5 mmHg). It was reduced with hydrogen (5% Pd/charcoal) in the presence of magnesium oxide (after Marshall and Walker, 1951), to give 2-chloro-4-methyl-pyrimidine. On distillation a forerun (*ca* 8%) was shown to be 4-methylpyrimidine by its n.m.r. spectrum.

2-Chloro-5-methylpyrimidine

2,4,6-Trichloro-5-methylpyrimidine was reduced with zinc dust and ammonia to 2-chloro-5-methylpyrimidine, b.p. 145-147°/70 mmHg (D.J. Brown and Lee, 1968).

4-Chloro-2-methylpyrimidin-6-one

4,6-Dihydroxy-2-methylpyrimidine (Henze *et al.*, 1952) was converted into the corresponding dichloro compound with phosphoryl chloride by the general method of D.J. Brown and Teitei (1964).

The dichloro compound (8.15 g, 0.05 mol) was added to N-sodium hydroxide solution (250 ml) and the mixture was stirred at room temperature for 3 h, during which time the solid dissolved. Acidification with 10N-hydrochloric acid, followed by refrigeration overnight, gave yellow crystals (2.28 g, 32%) m.p. 241-242° (Henze *et al.*, 1952, give yield 39% and m.p. 231.5-232°). The use of stronger alkali or a higher temperature resulted in a lower yield.

4-Mercapto-2-methylpyrimidin-2-one

Hydrogen sulphide was passed into a stirred mixture of 4-chloro-2-methylpyrimidin-6-one (8.70 g, 0.06 mol), sodium hydrogen sulphide (commercial; 6.0 g) and 2-ethoxyethanol (60 ml), first for 10 min at 25° and subsequently while boiling under reflux. The initial yellow slurry changed to a clear green solution on warming and after boiling for *ca* 30 min a bright yellow precipitate formed. The reaction was continued for twice the time taken for this precipitate to appear. The cooled mixture, adjusted to pH 2 with 5N-hydrochloric acid, gave 4-mercapto-2-methylpyrimidin-6-one (7.72 g, 91%), m.p. *ca* 301° (decomp.). Attempts to purify this compound failed (*cf.* Carrington *et al.*, 1955).

2-Methylpyrimidin-4(3*H*)-one

4-Mercapto-2-methylpyrimidin-6-one (4.0 g) was dissolved in the minimum volume of hot N-ammonia and boiled under reflux with Raney nickel (12 g, weighed wet) for 45 min. The filtered solution was evaporated to give the required pyrimidinone as a pale pink powder (2.93 g, 95%), m.p. 212.5-213° after sublimation at 115°/0.2 mmHg (den Hertog *et al.*, 1965: 212.5-213°) and pK_a (20°): 2.73±0.04 (anal. λ 290 nm)(Found: C, 54.5; H, 5.5; N, 25.45. Calc. for $C_5H_6N_2O$: C, 54.5; H, 5.4; N, 25.55%).

Preparation of this compound by a primary synthesis (den Hertog *et al.*, 1965: < 20% yield) from acetamidine and crude ethyl sodioformylacetate [which contains *ca* 33% ethyl sodioacetoacetate (Cogon, 1941)] followed by purification of the product from the by-product, 2,4-dimethylpyrimidin-6-one, was found to be less satisfactory than the above method.

4-Chloro-2-methylpyrimidine

2-Methylpyrimidin-4-one (2.53 g, 0.023 mol) and phosphoryl chloride (10 ml) were boiled under reflux for 1.5 h. The excess of phosphoryl chloride was removed by distillation under reduced pressure, and the residue was added to crushed ice (*ca* 50 g) with stirring. The mixture was extracted with ether; the extract, washed with dilute sodium bicarbonate solution and dried ($MgSO_4$), was evaporated under reduced pressure to give a crystalline residue which was at once sublimed (35^{o}/1.0 mmHg) to give colourless crystals of the chloromethylpyrimidine (1.91 g, 65%), m.p. 59-60^{o} [Chapman and Rees, 1954: 56.5-57^{o} (petrol)] (Found: Cl, 27.8. Calc. for $C_5H_5ClN_2$: Cl, 27.6%).

4-Chloro-5-methylpyrimidine

This was prepared in a manner similar to that for its 2-methyl isomer. 4,6-Dichloro-5-methylpyrimidine (D.J. Brown and Teitei, 1964) was refluxed with 1.25N-sodium hydroxide solution for 2.5 h. The cooled mixture, after filtering and extracting with ether (discarding the

extract), was acidified with 10N-hydrochloric acid. Refrigeration overnight gave 4-chloro-5-methylpyrimidin-6-one (68%), m.p. 206-207° (D.J. Brown and Teitei, 1964: 202-203°). An attempt to reduce this pyrimidine directly with hydrogen (10% Pd/charcoal) gave only starting material.

The chloropyrimidinone was converted, as for the 2-methyl isomer, into the corresponding mercapto compound (reaction time 5 h; yield 75%). After crystallisation from water (with active charcoal) it had m.p. *ca* 233° (decomp.) (D.J. Brown and Teitei, 1964: *ca* 200°) (Found: S, 22.6. Calc. for $C_5H_6N_2OS$: 22.6%). This material was desulphurised as before with Raney nickel, to give 5-methylpyrimidin-4-one (83%), m.p. 154-155° after sublimation at 115°/0.2 mmHg (Williams *et al.*, 1937: 153-154°). Treatment of the pyrimidinone with phosphoryl chloride, gave 4-chloro-5-methylpyrimidine as a colourless crystalline solid rapidly turning yellow; sublimation (35°/1.0 mmHg) gave colourless crystals which also decomposed: after *ca* 15 min the sublimate was odourless and completely soluble in water.

4,6-Dimethylpyrimidine-2(1*H*)-thione

This was prepared by a primary synthesis from thiourea and acetylacetone; it had m.p. 210-211° (Hale and Williams, 1915; Boarland and McOmie, 1952: m.p. 209-210°).

4-Methylpyrimidine-2(1*H*)-thione

Prepared by a primary synthesis from thiourea and 1,1-dimethoxybutan-3-one, this pyrimidine had m.p. 252° (decomp.) [Burness, 1956: 259° (pre-heated bath; purified sample)].

5-Methylpyrimidine-2(1*H*)-thione

1-Methyl-2-dimethylaminoacrolein was prepared from the reaction between propionaldehyde diacetal (Vogel, 1956, p.327) and a Vilsmeier dimethylformamide/phosgene adduct (Bredereck, Herlinger, and Renner, 1960). It was condensed with thiourea in ethanolic sodium ethoxide to give 5-methylpyrimidine-2-thione, m.p. 236-238° (Bredereck, Herlinger, and Sweizer, 1960: m.p. 234-235°).

2,4-Dimethylpyrimidine-6(1*H*)-thione

This was prepared by the action of phosphorus pentasulphide on 2,4-dimethylpyrimidin-6-one in pyridine; it had m.p. 232-234° (decomp.) (D.J. Brown and Foster, 1966: m.p. 233-234°).

4-Methylpyrimidine-6(1*H*)-thione

Prepared in the same way as the dimethyl homologue, this had m.p. 245° (decomp.) [Marshall and Walker, 1951 (from the reaction between thiourea and 4-chloro-6-methylpyrimidine): m.p. 255-260° (decomp.)].

Potassium pyrimidinesulphonates

(a) From the action of aqueous potassium sulphite on the corresponding chloro compound.

Potassium 2,4-dimethylpyrimidine-6-sulphonate

4-Chloro-2,6-dimethylpyrimidine (1.45 g, 0.01 mol) was added to a solution of freshly prepared potassium sulphite dihydrate (1.94 g, 0.01 mol) in water (10 ml), preadjusted (if necessary) to pH 7 by the addition of potassium carbonate. The mixture was boiled under reflux for 20 min, after which time the smell of the chloropyrimidine was no longer apparent, and then evaporated. The residue was dehydrated by admixture with chloroform (10 ml) and subsequent distillation.

Extraction of the residue by boiling anhydrous methanol (3 x 100 ml) and evaporation of the extracts gave potassium 2,4-dimethylpyrimidine-6-sulphonate (> 70%), m.p. *ca* 326° (decomp.) after crystallisation from aqueous ethanol and drying at 80°/0.1 mmHg (Found: C, 31.9; H, 3.4; K, 17.1; S, 14.4. $C_6H_7KN_2O_3S$ requires C, 31.8; H, 3.1; K, 17.3; S, 14.15%).

This compound was found to be less water soluble than other pyrimidinesulphonates prepared and it crystallised directly from the reaction mixture after ice-cooling (*cf.* Ochiai and Yamanaka, 1955).

A similar method (optimum reflux time given) was used to prepare the following pyrimidinesulphonates from the corresponding chloro compounds. The sulphonates were more generally dried for analysis at 110-120°. Aqueous ethanolic solutions of several of the salts formed gels during recrystallisation; in these cases, water was used.

Potassium 4,6-dimethylpyrimidine-2-sulphonate (reflux time 2 h; yield 51%) had m.p. 292-293° (decomp.) (Found: C, 31.45; H, 3.0; K, 16.9; N, 12.35; S, 14.05. $C_6H_7KN_2O_3S$ requires C, 31.8; H, 3.1; K, 17.3; N, 12.4; S, 14.15%).

Potassium 4,5-dimethylpyrimidine-6-sulphonate (reflux time 60 min) had m.p. 331° (decomp.) (Found: C, 32.3; H, 3.05; K, 17.0; N, 12.2; S, 14.1. $C_6H_7KN_2O_3S$ requires C, 31.8; H, 3.1; K, 17.3; N, 12.4; S, 14.15%).

Potassium 4,5-dimethylpyrimidine-2-sulphonate (reflux time 5 h, yield 74%) had m.p. 314° (decomp.) (Found: K, 17.3; S, 14.05. $C_6H_7KN_2O_3S$ requires K, 17.3; S, 14.15%).

Potassium 4-methylpyrimidine-2-sulphonate (reflux time 40 min) had m.p. 290-295° (decomp.) (Found: K, 18.2; S, 15.1. $C_5H_5KN_2O_3S$ requires K, 18.4; S, 15.1%).

The following sulphonates were prepared similarly but could not be separated from associated potassium chloride. Specimens with the compositions given below showed no sign of organic impurities (t.l.c.: 10% ethanol in chloroform; u.v., i.r., and ^{1}H n.m.r. spectra). Those not prepared subsequently in an analytically pure form (by method b) were used for hydrolysis-rate and log ε measurements.

Potassium 2,4,5-trimethylpyrimidine-6-sulphonate (Found: K, 17.35; N, 11.05; S, 13.1. $C_7H_9KN_2O_3S$ + 3% KCl requires K, 17.35; N, 11.3; S, 12.95%).

Potassium 4-methylpyrimidine-6-sulphonate (Found: C, 23.0; H, 2.0; N, 10.6; S, 11.95. $C_5H_5KN_2O_3S$ + 20.2% KCl requires C, 22.6; H, 1.9; N, 10.5; S, 12.05%).

Potassium 5-methylpyrimidine-2-sulphonate (Found: C, 26.75; H, 2.5; N, 12.7; S, 14.3. $C_5H_5KN_2O_3S$ + 5% KCl requires C, 26.85; H, 2.3; N, 12.5; S, 14.35%).

Potassium 2-methylpyrimidine-4-sulphonate (Found: C, 25.6; H, 2.05; N, 11.6; S, 13.7. $C_5H_5KN_2O_3S$ + 9.5% KCl requires C, 25.6; H, 2.15; N, 11.9; S, 13.7%).

Potassium pyrimidine-2-sulphonate

Only a crude sample of this salt could be prepared by this method: the best specimen contained *ca.* 9% pyrimidin-2-one (as revealed by t.l.c. and u.v. absorption at 296 nm) as well as potassium chloride. It was later

prepared in a pure state by the oxidation of pyrimidine-2-thione.

(b) By permanganate oxidation of the corresponding pyrimidinethiones.

Potassium 4,6-dimethylpyrimidine-2-sulphonate

Aqueous 0.05M-potassium permanganate was added dropwise to a shaken slurry of 4,6-dimethylpyrimidine-2-thione (0.70 g, 0.005 mol) in 50% aqueous ethanol(20 ml) until a pink colour persisted for 10-15 sec (difficult to see because of the thick precipitate of manganese dioxide). After 10 min the manganese dioxide was filtered off and washed with 50% aqueous ethanol. The combined filtrate and washings were evaporated and the last traces of water were removed by co-distillation with chloroform. A solution of the residue (0.73 g, 65%) in boiling anhydrous methanol was filtered and evaporated. Recrystallisation from aqueous ethanol gave potassium 4,6-dimethylpyrimidin-2-sulphonate, m.p. 295° (decomp.), identified with authentic material [see method (a)] by i.r. spectra (Found: C, 31.65; H, 3.1; K, 17.4; S, 13.9. Calc. for $C_6H_7KN_2O_3S$: C, 31.8; H, 3.1; K, 17.3; S, 14.1%).

Potassium 5-methylpyrimidine-2-sulphonate

5-Methylpyrimidine-2-thione (0.63 g, 0.005 mol) was oxidised as above. After filtration the manganese dioxide was washed with water alone to prevent leaching of small amounts of the water-insoluble disulphide present

as a by-product. The crude product (0.80 g, 76%) was dissolved in a minimum quantity of water and filtered from traces of disulphide. Evaporation of the filtrate and recrystallisation from aqueous ethanol gave potassium 5-methylpyrimidine-2-sulphonate, decomposing above 310° and identical in i.r. spectra with the salt-containing specimen described in method (a) (Found: C, 28.1; H, 2.2; S, 15.1. $C_5H_5KN_2O_3S$ requires C, 28.3; H, 2.4; S, 15.1%).

Potassium 4-methylpyrimidine-6-sulphonate

This was prepared as above from 4-methylpyrimidine-6-thione (0.63 g, 0.005 mol). The filtrate after removal of manganese dioxide was contaminated with colloidal manganese dioxide which coagulated on evaporation and was removed by dissolution of the residue in cold water and filtration. Subsequent evaporation gave potassium 4-methylpyrimidine-6-sulphonate (> 95%), m.p. 259-260° (Found: K, 18.6; S, 14.8. $C_5H_5KN_2O_3S$ requires K, 18.4; S, 15.1%).

Potassium pyrimidine-2-sulphonate

Pyrimidine-2-thione (0.56 g, 0.005 mol) was oxidised at *ca* 5°. (With the more reactive thiones oxidation was accompanied by an unacceptable temperature rise which necessitated ice-cooling.) Disulphide was removed from the crude product by extraction with chloroform; and traces of manganese dioxide by dissolution of the residue in a minimum of hot aqueous ethanol and filtering. On

cooling, the filtrate gave potassium pyrimidine-2-sulphonate (0.73 g, 74%), m.p. 328° (decomp.) (Found: C, 23.9; H, 1.4; K, 19.9; N, 13.8; S, 15.9. $C_4H_3KN_2O_3S$ requires C, 24.2; H, 1.5; K, 19.7; N, 14.1; S, 16.2%).

Potassium pyrimidine-4-sulphonate

Pyrimidine-4-thione (0.56 g, 0.005 mol)(Armarego, 1965) gave, when oxidised similarly to its isomer above, potassium pyrimidine-4-sulphonate (0.95 g, 96%), m.p. 330° (decomp.)(Found: C, 24.5; H, 1.6; K, 19.5; N, 14.1; S, 15.9. $C_4H_3KN_2O_3S$ requires C, 24.2; H, 1.5; K, 19.7; N, 14.1; S, 16.2%).

Sodium 2,6-dimethylpyrimidine-4-sulphonate

This was prepared according to Ochiai and Yamanaka (1955) by the action of aqueous sodium sulphite on the corresponding chloropyrimidine. The product was the anhydrous salt (78%), m.p. 284-285° (decomp.)(Ochiai and Yamanaka: Dihydrate; m.p. 285°)(Found: C, 33.85; H, 3.4; Na, 10.6; S, 15.1. $C_6H_7N_2NaO_3S$ requires C, 34.25; H, 3.4; Na, 10.95; S, 15.25%).

Lithium 4,6-dimethylpyrimidine-2-sulphonate

The product obtained from the action of aqueous lithium sulphite on 2-chloro-4,6-dimethylpyrimidine was heavily contaminated with lithium chloride.

Potassium sulphite dihydrate

Commercial material proved unsatisfactory for the preparation of the pyrimidinesulphonates. Accordingly, sulphur dioxide was passed into a stirred mixture of potassium carbonate (50 g) in water (50 ml) until the supernatant liquid reached pH 6. After cooling in ice, the solid was filtered off and well pressed. It was dried *in vacuo* over calcium chloride and stored in an air-tight bottle. The shelf-life was *ca* 3 months.

Lithium sulphite was prepared in a similar manner. (*cf.* preparation of sodium sulphite; Parkes and Mellor, 1939).

Bis(4,6-dimethylpyrimidin-2-yl) disulphide

4,6-Dimethylpyrimidine-2-thione (0.25 g) was dissolved in 0.2M-potassium hydroxide (10 ml) and shaken for 2 min with a solution of iodine (0.3 g) in M-potassium iodide (10 ml). The precipitate was filtered off and washed thoroughly with water at 0^{o}. The disulphide (96%; from methanol) had a sharp m.p. within the range 150-155^{o}, according to the rate of heating (Found: C, 51.6; H, 5.1; N, 20.1; S, 23.05. M^{+} 278. $C_{12}H_{14}N_4S_2$ requires C, 51.5; H, 5.2; N, 20.3; S, 22.7%. M^{+} 278). U.v. absorption maxima (MeOH):- 241(4.30); 268(3.93). The yield decreased if stronger alkali or a longer reaction time was employed.

This disulphide was the only product isolated when a stirred slurry of the thione in water was treated with freshly prepared bromine water until a colouration persisted for 10-15 sec.

Di(4-methylpyrimidin-2-yl) disulphide

4-Methylpyrimidine-2-thione hydrochloride (0.25 g) in water (10 ml) was adjusted to pH 7 with saturated aqueous sodium hydrogen carbonate. A 3% solution of iodine in M-potassium iodide was added dropwise with stirring until a colouration persisted for 10-15 sec. The mixture was stirred for a further 2 min and then fawn crystals of the disulphide were filtered off and washed with water at 0^{o}. The disulphide (0.14 g, 73%) after recrystallisation from methanol had m.p. 104-104.5^{o} (Found: N, 22.15; S, 25.8. $C_{10}H_{10}N_4S_2$ requires N, 22.4; S, 25.6%).

Di(5-methylpyrimidin-2-yl) disulphide

Treatment of 5-methylpyrimidine-2-thione as its 4-methyl isomer above, gave the disulphide (88%), m.p. 178-179^{o} (from ethanol)(Found: C, 47.7; H, 3.8; N, 22.6; S, 25.5. $C_{10}H_{10}N_4S_2$ requires C, 48.0; H, 4.0; N, 22.4; S, 25.6%).

Dipyrimidin-2-yl disulphide

(1) Similar oxidation of pyrimidine-2-thione gave this disulphide (85%), m.p. 135-136^{o} (from methanol; *cf.* Batterham and Bigum, 1972: 141^{o})(Found: C, 43.45; H, 2.55; N, 24.9; S, 28.65. M^{+} 222. $C_8H_6N_4S_2$

requires C, 43.2; H, 2.7; N, 25.2; S, 28.9%. M^+ 222).

(2) A solution of potassium permanganate (0.5 g) in acetone (30 ml) was added in drops to a stirred solution of the thione (0.25 g) in acetone until colouration persisted for 10-15 sec. The solution, after filtration and evaporation, gave colourless crystalline plates shown by mixed m.p. and i.r. spectrum to be the disulphide (0.16 g, 64%).

4,6-Dimethylpyrimidine-2-sulphenamide

(After the general method of Hurley and Robinson, 1965). Commercial 1.4 M-sodium hypochlorite solution (*ca* 5% available chlorine; 15 ml) was cooled to < 0° in an ice/salt bath and added to similarly cooled 1.4 M-ammonia (40 ml). (The order of addition is important to maintain an excess of ammonia and so prevent the formation of nitrogen trichloride.) The resulting solution of chloramine was mixed with a solution of 4,6-dimethylpyrimidine-2-thione (1.4 g; 0.01 mol) in 2 M-potassium hydroxide (5 ml), also at < 0°. The mixture was stirred until it warmed to room temperature (*ca* 15 min). The crystalline solid was filtered off and washed with a little ice-water. After drying at 25° *in vacuo* and sublimation (90°/1 mmHg) the colourless crystals of the sulphenamide (25%) had m.p. 99.5-100° (Found: C, 46.4; H, 6.15; N, 27.0; S, 20.95. $C_6H_9N_3S$ requires C, 46.45; H, 5.85; N, 27.1; S, 20.65%), u.v. absorption maxima (MeOH):- 251(4.04),

282(3.51). When 5 M-ammonia was substituted for potassium hydroxide above, the crude product gave sulphenamide (11%) on sublimation; the residue in methanol, after treatment with charcoal and concentration to small volume, gave bis(4,6-dimethylpyrimidin-2-yl) disulphide (59%). identified by i.r. spectra and a mixed m.p. with authentic material.

Oxidation of 4,6-Dimethylpyrimidine-2-sulphenamide

(*Cf.* Greenbaum, 1954) Aqueous 0.05M-potassium permanganate was added in drops to a shaken solution of the sulphenamide (0.1 g) in 50% aqueous ethanol (5 ml) until colouration persisted for 10-15 sec. Filtration, to remove manganese dioxide, and evaporation gave a residue which was extracted with boiling ethanol (4 x 5 ml). The extract, after evaporation and crystallisation from 50% aqueous ethanol, yielded a few crystals, m.p. 161.5-162^{o} shown by i.r. spectrum and mixed m.p. to be bis(4,6-dimethylpyrimidin-2-yl) disulphide. The mother liquor was shown by t.l.c. (10% ethanol in chloroform; isobutyl methyl ketone) to contain two major components: the disulphide and, by comparison with an authentic sample, 4,6-dimethylpyrimidine-2-sulphonamide. It was estimated that both products were formed in less than 5% yield.

4,6-Dimethylpyrimidine-2-sulphonyl fluoride

A steady stream of chlorine was passed for *ca* 30 min into a stirred mixture of 4,6-dimethylpyrimidine-2-thione (7.0 g; 0.05 mol), potassium hydrogen difluoride (39 g; 0.5 mol), water (25 ml) and methanol (25 ml) maintained in a 250 ml polypropylene flask at < -10^{o} (solid CO_2/CCl_4). The yellow colour of the thione quickly faded and a thick white precipitate formed. The end of the reaction was confirmed by a lack of tendency for the temperature to rise and by immediate bleaching of litmus paper by a drop of the mixture. The slurry was added immediately to crushed ice (*ca* 150 g). The solid was filtered off and washed with water at 0^{o} until the washings were > pH 3. Dried *in vacuo*, the sulphonyl fluoride (6.6 g, 78%) had m.p. 57-58^{o} (from diethyl ether)(Found: C, 38.05; H, 3.9; S, 17.0. $C_6H_7FN_2O_2S$ requires C, 37.9; H, 3.7; S, 16.9%).

When potassium fluoride in water was used instead of the acid salt in water/methanol the product was pale yellow, darkened on standing, and evolved sulphur dioxide (*cf.* Beaman and Robins, 1961).

4-Methylpyrimidine-2-sulphonyl fluoride

4-Methylpyrimidine-2-thione (2.52 g; 0.02 mol) was treated as the dimethyl homologue above to the stage of addition to crushed ice. The precipitate on washing with water at 0^{o} melted and the material was recovered from the filtrate by extraction with ether (4 x 100 ml). After washing the extract with a little aqueous sodium hydrogen

carbonate, it was dehydrated ($CaSO_4$), and evaporation gave the sulphonyl fluoride as an oil (2.63 g, 75%), which crystallised below 0^o, and was further purified by distillation (b.p. 101-102^o/0.3 mmHg)(Found: C, 34.3; H, 2.6; S, 18.6. $C_5H_5FN_2O_2S$ requires C, 34.4; H, 2.85; S, 18.2%).

5-Methylpyrimidine-2-sulphonyl fluoride

Prepared as the 4-methyl isomer above from 5-methylpyrimidine-2-thione (2.52 g, 0.02 mol), the crude product was washed through the filter with ether into the filtrate, which was then extracted as before (in this way undissolved potassium hydrogen difluoride, and small amounts of disulphide and unreacted thione were removed). Evaporation of the ethereal extract (after washing with dilute sodium hydrogen carbonate and dehydration) gave the sulphonyl fluoride as colourless crystals (3.53 g, quant.), m.p. 76-77^o (from ethanol)(Found: C, 34.5; H, 2.9; N, 15.6; S, 18.5. $C_5H_5FN_2O_2S$ requires C, 34.4; H, 2.85; N, 15.9; S, 18.2%).

Pyrimidine-2-sulphonyl fluoride

Pyrimidine-2-thione (2.24 g, 0.02 mol) was treated as the 5-methyl compound above to give the sulphonyl fluoride (2.92 g, 90%) as an oil which crystallised on cooling. It had m.p. 57-58^o (from ethanol)(Found: N, 17.0; S, 19.9. $C_4H_3FN_2O_2S$ requires N, 17.25; S, 19.8%).

4,6-Dimethylpyrimidine-2-sulphonamide

(1) 4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0.5 g) was added to liquid ammonia (*ca* 5 ml). After 5 min the mixture was filtered and allowed to evaporate. The residual sulphonamide (0.4 g, 82%) had m.p. 198-199° (from aqueous methanol) (Roblin and Clapp, 1950: 200°) (Found: N, 22.45. Calc. for $C_6H_9N_3O_2S$: N, 22.45%).

(2) 4,6-Dimethylpyrimidine-2-thione (1.4 g, 0.01 mol) in N-potassium hydroxide (10 ml) was maintained at *ca* -10° (ice/salt) while a stream of chlorine was passed in for 35 min. The solid was filtered off immediately, washed with ice-water, and added in portions to liquid ammonia (*ca* 10 ml). A small amount of undissolved disulphide (identified by mixed m.p.) was filtered off. The residue from evaporation recrystallised from water to give the same sulphonamide (0.82 g, 44%) as in (1) above.

(3) The procedure was like that for (2) but 0.5 N-potassium hydroxide was used and the chlorine passed for 20 min. A large amount of disulphide together with 13% of sulphonamide was obtained.

(4) The preparation was repeated as in (2) but using a neutral solution with or without a trace of iron(III) chloride present (Pala, 1958): up to 10% of sulphonamide was obtained.

When the reaction was carried out in hydrochloric or acetic acid (Roblin and Clapp, 1950), up to 50% of the disulphide was obtained, unaccompanied by sulphonamide.

4-Methylpyrimidine-2-sulphonamide

4-Methylpyrimidine-2-sulphonyl fluoride (2.15 g) was added to liquid ammonia as in method (1) above to obtain the sulphonamide (1.59 g, 79%), m.p. 162.5-163° (from aqueous ethanol)(Found: C, 35.05; H, 4.05; N, 24.0; S, 18.2. $C_5H_7N_3O_2S$ requires C, 35.0; H, 4.1; N, 24.25; S, 18.5%). [From some batches another crystalline form (which melted at 151°, resolidified, and remelted at 163°) was isolated; its identity was confirmed by mixed m.p. with a sample of the higher melting material (Found: N, 24.3; S, 18.6%)].

5-Methylpyrimidine-2-sulphonamide

This was made as the 4-methyl isomer from 5-methylpyrimidine-2-sulphonyl fluoride. After recrystallising twice from aqueous ethanol the sulphonamide had m.p. 151-152° (Found: C, 34.9; H, 4.2; N, 24.05; S, 18.6. $C_5H_7N_3O_2S$ requires C, 35.0; H, 4.1; N, 24.25; S, 18.5%).

Pyrimidine-2-sulphonamide

Prepared as the 4-methyl compound, but from pyrimidine-2-sulphonyl fluoride, the sulphonamide (from aqueous ethanol) had m.p. 180.5-181° (bubbling) [Roblin and Clapp, 1950: 180.5-181° (bubbling)].

4,6-Dimethylpyrimidine-2-*N*-ethylsulphonamide

4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0.5 g) was added to 30% ethanolic ethylamine (5 ml). After standing for 5 min the solution was evaporated. The

residue was triturated with a little cold water, and recrystallised from aqueous ethanol to give the ethylsulphonamide (*ca* 10%), m.p. 130.5-131.5° (from ethanol)(Found: C, 44.9; H, 6.3; S, 14.9. $C_8H_{13}N_3O_2S$ requires C, 44.5; H, 6.1; S, 14.9%).

4,6-Dimethylpyrimidine-2-*NN*-diethylsulphonamide

A mixture of 4,6-dimethylpyrimidine-2-sulphonyl fluoride (0.5 g) in diethylamine (5 ml) was boiled under reflux for 5 min. The cooled mixture was filtered and the filtrate evaporated to give a crystalline residue of the diethylsulphonamide. Crystallisation from aqueous ethanol gave colourless crystals, m.p. 59.5-60.5° (0.64 g, quant.). The compound was shown to be pure by t.l.c. (5% diethyl ether/benzene) and the spot absorbed black under 365 nm u.v. light (*cf.* 2-diethylamino-4,6-dimethylpyrimidine which fluoresces blue)(Found: C, 49.5; H, 7.4; N, 17.3; S, 13.3. $C_{10}H_{17}N_3O_2S$ requires C, 49.4; H, 7.0; N, 17.3; S, 13.2%).

4,6-Dimethylpyrimidine-2-sulphonomorpholide

A mixture of 4,6-dimethylpyrimidine-2-sulphonyl fluoride (0.1 g) in morpholine (1 ml) was heated at 100° for 30 min. The mixture was evaporated and the residue, in ether, was chromatographed through silica (Woelm, dry column grade), eluting with ether to give one fraction which on evaporation gave the sulphonomorpholide (125 mg, 93%), m.p. 159-160° (from petrol/diethyl ether)(Found: C, 46.6; H, 6.0; N, 16.3; S, 12.45. $C_{10}H_{15}N_3O_3S$ requires C, 46.65; H, 5.9; N, 16.3; S, 12.45%).

4,6-Dimethylpyrimidine-2-*NN*-di-isopropylsulphonamide

A mixture of 4,6-dimethylpyrimidine-2-sulphonyl fluoride (0.2 g) in di-isopropylamine (5 ml) was boiled under reflux for 4 h; a copious white precipitate formed after 15 min. After standing overnight the amine was evaporated and the residue crystallised from methanol to yield colourless crystals of the sulphonamide (94 mg, 31%). The mother liquor was purified by elution from a silica column first with chloroform (rejected) and then with ethanol. On concentration, the ethanolic eluate gave more of the sulphonamide (146 mg, 48%; total yield 79%), m.p. *ca* 235° (decomp.) (from aqueous ethanol) [Found (from material dried at 25°): C, 49.6; H, 8.3; N, 14.45. $C_{12}H_{21}N_3O_2S,H_2O$ requires C, 49.8; H, 8.0; N, 14.5%)].

4,6-Dimethylpyrimidine-2-sulphonohydrazide

Hydrazine hydrate (0.5 ml) was added in drops to an agitated solution of 4,6-dimethylpyrimidine-2-sulphonyl fluoride (1.0 g) in methanol (5 ml) maintained at -10° to -15°. The mixture was filtered at once. [The filtrate contained 2-hydrazino-4,6-dimethylpyrimidine: evaporation, followed by trituration of the residue with water and extraction with chloroform, then evaporation of the chloroform solution gave 2-hydrazino-4,6-dimethylpyrimidine (70 mg, 39%), m.p. 161.5-162° (after sublimation; 100°/0.2 mmHg) identified with authentic material by mixed m.p.]. The solid, dissolved in chloroform, was

washed with a little water, and the chloroform layer evaporated to give the sulphonohydrazide (0.42 g, 40%), m.p. 124-125° (bubbling)(from ethanol) (Found: C, 35.65; H, 5.2; S, 15.8. $C_6H_{10}N_4O_2S$ requires C, 35.65; H, 5.0; S, 15.85%).

4,6-Dimethylpyrimidine-2-*N*-isopropylidenesulphonohydrazide

The above sulphonohydrazide (0.05 g) was boiled under reflux in acetone (2 ml) for 5 min. Filtration and evaporation gave a solid which was dissolved in chloroform, washed with water, and recovered by evaporation. The *N*-isopropylidenesulphonohydrazide (55 mg, 92%) had m.p. 170.5-171° (from ethanol)(Found: C, 44.8; H, 6.25; N, 22.75; S, 13.2. $C_9H_{14}N_4O_2S$ requires C, 44.6; H, 5.85; N, 23.1; S, 13.25%).

2-Hydrazino-4,6-dimethylpyrimidine

(1) A mixture of 4,6-dimethylpyrimidine-2-sulphonohydrazide, -2-sulphonamide, or -2-sulphonyl fluoride (0.5 g) with hydrazine hydrate (2 ml) in methanol (10 ml) was boiled under reflux for 1 h. After evaporation, the residue was mixed with water (25 ml) and extracted with chloroform (4 x 15 ml). Evaporation of the extract and sublimation (100°/0.2 mmHg) gave the 2-hydrazinodimethylpyrimidine (>95%), m.p. 162° (Boarland, McOmie and Timms, 1952: 165°)(Found: C, 52.25; H, 7.65; N, 40.55. Calc. for $C_6H_{10}N_4$: C, 52.2; H, 7.25; N, 40.55%), u.v. absorption maxima (MeOH): 235(4.03), 263(3.89), 293(3.57).

(2) Potassium 4,6-dimethylpyrimidine-2-sulphonate (0.4 g) was treated with hydrazine as above but using 50% aqueous ethanol as solvent. The mixture was evaporated to half its volume and water (20 ml) was added before extraction with chloroform. The sublimed product was identified with that in (1) by mixed m.p.

4-Hydrazino-2,6-dimethylpyrimidine

(1) Potassium 2,4-dimethylpyrimidine-6-sulphonate (0.5 g) underwent hydrazinolysis as its isomer above to give the 4-hydrazinodimethylpyrimidine (170 mg, 56%), m.p. 186-187° (Nagasa *et al.*, 1962: 186-187°)(Found: C, 52.5; H, 7.45; N, 40.05. $C_6H_{10}N_4$ requires C, 52.2; H, 7.25; N, 40.6%).

(2) A solution of the same sulphonate (0.5 g) and hydrazine sulphate (0.5 g) in 50% aqueous ethanol (10 ml) was adjusted to pH 7 by the addition of hydrazine hydrate. After boiling under reflux for 45 min, water (25 ml) was added, and the mixture was extracted with chloroform. Evaporation of the extract and sublimation gave the same product (100 mg, 41%) as in (1).

NN'-Bis(2,4-dimethylpyrimidin-6-yl)hydrazine

The unsublimed residue from method (2) above gave, after crystallisation from ethanol, a little *NN*'-bis(dimethylpyrimidin-6-yl)hydrazine, m.p. 255-256°, M^+ = 244.14372 ($C_{12}H_{16}N_6$ requires M^+ 244.14364), and u.v. absorption maxima (MeOH):- 235(4.23), 272(4.08), [*cf.* 2-propyl homologue prepared by Miller and Rose, 1963: 228(4.15), 273(4.05)].

2-Diethylamino-4,6-dimethylpyrimidine

4,6-Dimethylpyrimidine-2-sulphonyl fluoride (1.0 g) and diethylamine (10 ml) were heated in a sealed tube at 150° for 4 h. Extraction of the tube contents with ether followed by evaporation gave a crystalline material shown by t.l.c. (5% diethyl ether/benzene) to contain one major component of the same R_f value and fluorescence (blue) as a specimen (D.J. Brown and Lyall, 1965) of 2-diethylamino-4,6-dimethylpyrimidine. A minor component had the same R_f value and u.v. absorption as a specimen of 4,6-dimethylpyrimidine-2-sulphonamide. Sublimation (25°/0.2 mmHg) yielded colourless crystals (280 mg, 60%), m.p. 33-34° apparently pure on t.l.c. However, a mixed m.p. with an authentic specimen (m.p. 41°) melted at 33-34°, partially resolidified, and remelted at 37°. The i.r. spectra of both specimens were identical.

2-Hydrazino-5-methylpyrimidine.

Hydrazine hydrate (2.5 ml) was added to 5-methylpyrimidine-2-sulphonyl fluoride (0.18 g, 0.001 mol) in methanol (2.5 ml). After a vigorous reaction, the mixture was boiled under reflux for 30 min. The residue from partial evaporation was added to water (10 ml) and the solution adjusted to pH 8 with hydrochloric acid. Extraction with chloroform (4 x 15 ml), evaporation of the extract, and sublimation (80°/0.2 mmHg) gave the colourless hydrazinomethylpyrimidine (> 95%), m.p. 143-144° (Found: C, 48.5; H, 6.5; N, 45.2. $C_5H_8N_4$ requires C, 48.4; H, 6.5; N, 45.1%).

2-Azido-5-methylpyrimidine

5-Methylpyrimidine-2-sulphonyl fluoride (0.18 g, 0.001 mol) in methanol (0.5 ml) was added to sodium azide (65 mg, 0.001 mol) in water (0.3 ml). After the initial vigorous reaction the mixture was allowed to stand for 18 h during which time separation into 2 phases occurred; by the end of the reaction the lower phase had crystallised. The mixture was evaporated at 25°, extracted with anhydrous methanol, and the extract evaporated to small bulk. Two components were separated by preparative t.l.c. (5% methanol/chloroform): the azidomethylpyrimidine (74 mg, 55%) m.p. 123-123.5° [from ethanol/water (1:3)] (Found: C, 44.0; H, 3.8; N, 51.85. $C_5H_5N_5$ requires C, 44.4; H, 3.7; N, 51.8%), and a minor unidentified compound which differed (t.l.c.) from the corresponding sulphonamide.

2-Azido-4,6-dimethylpyrimidine

4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0.19 g, 0.001 mol) in methanol (0.5 ml) was added to a solution of sodium azide (65 mg, 0.001 mol) in water (0.3 ml). The mixture was stirred at 50° for 1 h, and then allowed to stand overnight at 25°, during which time acicular crystals appeared. The residue from evaporation of the mixture was extracted with anhydrous methanol, and the extract again reduced to dryness. Recrystallisation (with concentration) from ethanol/water (1:2) gave the bulk of the product (82 mg); submission of the mother liquors to

preparative t.l.c. (5% methanol/chloroform) separated more of the product (20 mg) from a by-product. The azidodimethylpyrimidine (102 mg, 69%) had m.p. 155-155.5° (Sirakawa, 1957: 153-154°) and the same i.r. spectrum as authentic material (Temple and Montgomery, 1965). The by-product (27 mg, 14%) after crystallisation from ether was shown to be 4,6-dimethylpyrimidine-2-sulphonamide by mixed m.p., t.l.c., and i.r. spectrum.

2-Methoxy-4,6-dimethylpyrimidine

4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0.5 g) and methanolic sodium methoxide [from sodium (0.1 g) and methanol (25 ml)] were boiled under reflux for 1.5 h. The residue from removal of solvent was diluted with water (10 ml) and extracted with chloroform (5 x 15 ml). The oil obtained on evaporation of the extract was triturated with aqueous sodium hydrogen carbonate and re-extracted into ether. After filtration through alumina, the ether extract was evaporated to give the methoxypyrimidine (0.2 g, 56%). It was identified with authentic material (D.J. Brown and Foster, 1966, after Angerstein, 1901) by its i.r. spectrum and as its picrate (Yamanaka, 1959), m.p. and mixed m.p. 137-138°.

The sulphonyl fluoride was recovered unchanged after being boiled with anhydrous methanol under reflux at 5 h.

4,6-Dimethylpyrimidin-2(1*H*)-one

4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0.25 g) and water (2.5 ml) were boiled under reflux until the mixture was homogeneous (*ca* 45 min). The solution was

adjusted to pH 2 with sodium hydroxide and evaporated to dryness, using azeotropic distillation with chloroform to remove the last traces of water. The solid was extracted in a Soxhlet apparatus by ethyl acetate. Evaporation of the extract and recrystallisation of the residue from ethanol gave the pyrimidinone (76 mg, 47%), identified with authentic material (from the hydrochloride; see p. 85) by mixed m.p. 199-200°, and i.r. spectrum.

2,4-Dimethylpyrimidin-6(1*H*)-one

Potassium 2,4-dimethylpyrimidine-6-sulphonate (0.25 g) was added to 2.85 N-hydrochloric acid (20 ml). After 18 h at 25° the mixture was adjusted to pH 6 and treated as in the previous experiment. The pyrimidinone (110 mg, 80%) was identified by its i.r. spectrum and mixed m.p. (199-200°) with authentic material. Similar treatment of the sulphonate in N-sodium hydroxide at 40° gave an identical product (66%).

PYRIDINE

Pyridine-2-sulphonic acid

This was prepared by the literature methods (den Hertog *et al.*, 1958; Evans and H.C. Brown, 1962) using oxidation of pyridine-2-thione with nitric acid. To achieve a satisfactory reaction it was necessary to use brown rather than colourless nitric acid. The product had m.p. 255.5-256° (from absolute ethanol) [Evans and H.C. Brown, 1962: 251-252° (from 95% ethanol)].

PYRAZOLO[3,4-*d*]PYRIMIDINES

3-Amino-4-cyanopyrazole

(*Cf.* Wellcome Foundation Ltd., 1958). Ethoxymethylenemalononitrile (30.5 g, 0.5 mol)(prepared after Huber, 1943) was added in portions to hydrazine hydrate (25 g, 0.5 mol) in ethanol (20 ml) with cooling. After heating on the steambath for 2 h the mixture was diluted with hot water (50 ml) and allowed to cool gradually to 0^{o}. Pale orange crystals (23 g) were removed. The filtrate was evaporated. The residue was mixed with water (10 ml) and chilled to obtain a second crop (3.5 g) (total yield > 95%). The product was treated in alcohol-water (1:4) with charcoal. The resulting material, after recrystallisation from ethanol, was a pale fawn crystalline powder, m.p. 179-179.5^{o} (Robins, 1956: 174-175^{o}) (Found: C, 44.45; H, 3.8; N, 52.05. Calc. for $C_4H_4N_4$: C, 44.45; H, 3.7; N, 51.8%).

Pyrazolo[3,4-*d*]pyrimidine-4(5*H*)-thione

This was prepared according to Taylor *et al.*, 1966, by the action of triethyl orthoformate on 3-amino-4-cyanopyrazole followed by ring closure and thiation of the crude 4-cyano-3-ethoxymethyleneaminopyrazole with ethanolic sodium hydrogen sulphide.

When 2-ethoxyethanol was used instead of ethanol as a solvent, the reaction time could be reduced from 12 h to 4 h. The product (97%) darkened but did not melt by 360° [Taylor *et al.*: 354-356° (decomp.)]; pK_a -0.66 ± 0.04 (anal. λ 347 nm), 8.34 ± 0.05 and 11.65 ± 0.04 (anal. λ 300 nm) (Found: C, 39.3; H, 2.5; N, 36.8; S, 21.25. Calc. for $C_5H_4N_4S$: C, 39.45; H, 2.65; N, 36.8; S, 21.1%).

A sample of this material was converted into 4-methylthiopyrazolo[3,4-*d*]pyrimidine, m.p. 191-192° (Robins, 1956: 192°) which was hydrolysed to give a crude sample of "Allopurinol", pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one, by boiling under reflux in 6 N-hydrochloric acid for 1 h.

PURINES

2-Mercaptopurine

This was made after Albert and Brown (1954).

9-Methylpurine-6(1*H*)-thione

This was made after Robins and Lin (1957), from the reaction between 6-chloro-9-methylpurine and thiourea.

Potassium purine-6-sulphonate

Purine-6-thione (1.0 g) in 50% aqueous ethanol (20 ml) was oxidised with 0.05 M-potassium permanganate (*cf.* Doerr *et al.*, 1961) as for potassium 4,6-dimethylpyrimidine-2-sulphonate (p. 95) to give the purinesulphonate (0.89 g, 57% after crystallisation from water) (Found: K, 16.7. Calc. for $C_5H_3KN_4O_3S$: 16.4%).

Potassium purine-8-sulphonate

A similar oxidation of purine-8-thione (1.0 g) gave the purinesulphonate in almost quantitative yield. After crystallisation from water it decomposed without melting *ca* 330° (Found: C, 23.4; H, 2.0; N, 21.9; S, 12.5; K, 15.25. $C_5H_3KN_4O_3S,H_2O$ requires C, 23.4; H, 2.2; N, 22.0; S, 12.8; K, 15.05%).

Potassium 9-methylpurine-6-sulphonate

9-Methylpurine-6-thione (0.25 g) in alcohol (10 ml) was oxidised as above; the reaction was slow and required warming to *ca* 40° to initiate and sustain it. The purinesulphonate (0.27 g, 64%), after crystallisation from water, had m.p. >330° (Found: N, 21.25; S, 12.0; K, 14.7. $C_6H_5KN_4O_3S,H_2O$ requires N, 20.75; S, 11.9; K, 14.5%).

Purine-6-sulphonyl fluoride

This was prepared by the method of Beaman and Robins (1961)(Found: N, 27.7. Calc. for $C_5H_3FN_4O_2S$: N, 27.7%). When the compound was dried in air it became discoloured and the original colourless form could not be regained by recrystallisation from alcohol (with charcoal).

6-Hydrazinopurine

Hydrazine hydrate (0.2 ml, 0.004 mol) was added over 1 min to an ice-cooled and agitated slurry of purine-6-sulphonyl fluoride (0.2 g, 0.001 mol) in methanol (4 ml).

The clear solution deposited a few crystals over 3 min and was then warmed to 25°, when the crystals dissolved. After a total reaction time of 8 min the mixture was evaporated under reduced pressure at < 50°. The residue crystallised from aqueous ethanol to give the hydrazinopurine (150 mg, quant.), which decomposed *ca* 240° (from water) [Elion *et al.*, 1952: 244-245° (decomp.); Montgomery and Holum, 1957: 246-247.5° (decomp.)] and had the same i.r. spectrum as that reported by Montgomery and Holum (Found: C, 40.2; H, 4.4; N, 55.4. Calc. for $C_5H_6N_6$: C, 40.0; H, 4.05; N, 56.0%).

Purine-6-sulphonohydrazide

Hydrazine hydrate (0.2 ml, 0.004 mol) was added over 30 sec to an agitated slurry of purine-6-sulphonyl fluoride (0.2 g, 0.004 mol) in methanol (4 ml) cooled to < -10° (ice/salt). After a further 30 sec the mixture was adjusted to pH 5 with hydrochloric acid and allowed to warm to 25°. A crystalline precipitate of the sulphonohydrazide (80 mg, 37%) which slowly formed was filtered off: a sample decomposed *ca* 240° (Found: C, 26.05; H, 3.75; N, 35.8; S, 13.6. $C_5H_6N_6O_2S,H_2O$ requires C, 25.85; H, 3.5; N, 36.2; S, 13.8%).

Action of sodium methoxide on purine-6-sulphonyl fluoride

Purine-6-sulphonyl fluoride (0.4 g, 0.002 mol) and methanolic sodium methoxide [from sodium (0.1 g, *ca* 0.004 g atom) and anhydrous methanol (10 ml)] were

boiled under reflux for 3 h. The cooled mixture was diluted with water (2 ml) and adjusted to pH 6 with dilute hydrochloric acid. Cooling below 0^{o} gave a white precipitate, m.p. > 340^{o}, shown by its i.r. spectrum to be the crude 6-sulphonate (90 mg) and contaminated with sodium chloride (elemental analysis). The evaporated mother liquor was shown similarly to contain sulphonate (there were no indications of the presence of the corresponding hydroxy or methoxy compounds).

QUINAZOLINES

Quinazoline-4(3*H*)-thione

This was prepared after Fry *et al.* (1960) from the reaction between quinazolin-4-one and phosphorus pentasulphide in pyridine. The thione (94%) had m.p. 326-328^{o} (Fry *et al.*: 320-322^{o}) (Found: S, 19.4. Calc. for $C_8H_6N_2S$: S, 19.75%).

Quinazoline-2(1*H*)-thione

o-Aminobenzaldehyde (Smith and Opie, 1948) was fused with urea to yield quinazolin-2-one (Gabriel and Posner, 1895; Gabriel and Stelzner, 1896), which was treated with phosphoryl chloride and phosphorus pentachloride to give 2-chloroquinazoline (58%) (Albert and Barlin, 1962). Reaction of this material with sodium hydrogen sulphide in 2-ethoxyethanol (rather unsatisfactory), or better with thiourea followed by treatment with alkali, gave

the quinazolinethione (94%), m.p. 220-221° (Albert and Barlin, 1962: 230-231°) (Found: C, 58.9; H, 3.5; N, 17.7; S, 19.85; M^+ 162. Calc. for $C_8H_6N_2S$: C, 59.2; H, 3.7; N, 17.3; S, 19.8%; M^+ 162).

5,6,7,8-Tetrahydroquinazolin-4(3*H*)-one

[After the general method of McCasland and Bryce (1952), modified after the method of Hull *et al.* (1946) used to prepare 4,5-dimethylpyrimidin-6-one]. Formamidine acetate (5.2 g, 0.05 mol) and 2-ethoxycarbonylcyclohexanone (8.5 g, 0.05 mol) (Wade *et al.*, 1957) were added consecutively to ethanolic sodium ethoxide [from sodium (1.72 g, 0.075 g atom) and ethanol (50 ml)]. The mixture was shaken for a few minutes to mix it thoroughly, and it was allowed to stand at 25° for 3 days. After boiling under reflux for 4 h the mixture was cooled, diluted with a little water, and adjusted to *ca* pH 5 with hydrochloric acid. Extraction of the residue from evaporation (in a Soxhlet apparatus with ethyl acetate) gave the quinazolinone (6.5 g, 87%), m.p. 167-169° (from n-propanol) (Baker *et al.*, 1953: 162-164°) (Found: C, 63.7; H, 6.9; N, 18.55. Calc. for $C_8H_{10}N_2O$: C, 64.0; H, 6.7; N, 18.65%); pK_a (20°): 2.69 ± 0.03 and 9.64 ± 0.03 (anal. λ 285 nm); u.v. absorption maxima (H_2O):-

pH 12.5 (anion) : 234(3.92); 261(3.70)

pH 6.0 (neutral mol.): 234(3.83); 239(3.84); 256(3.82)

pH 0 (cation) : 239(3.99); *ca* 268sh.(3.58).

5,6,7,8-Tetrahydro-2-methylquinazolin-4(3*H*)-one

This was prepared essentially as for the unmethylated homologue above but using acetamidine hydrochloride [tech. (90%); 5.3 g, 0.05 mol]. Being insoluble in ethyl acetate, the residue from evaporation was extracted with n-propanol to yield the quinazolinone as its hydrochloride (6.18 g, 62%), m.p. 298-299° (decomp.)(Found: C, 54.0; H, 6.4; N, 14.1. $C_9H_{12}N_2O$,HCl requires C, 53.9; H, 6.5; N, 14.0%); pK_a (20°): 3.73±0.04 (anal. λ 245 nm) and 10.50±0.03 (anal. λ 285 nm); u.v. absorption maxima (H_2O):-

pH 12.5 (anion) : 234(3.88); 264(3.76)

pH 6.0 (neutral mol.): 236(3.82); 259(3.82)

pH 0 (cation) : 240(3.98); *ca* 264sh.(3.71).

5,6,7,8-Tetrahydroquinazoline-4(3*H*)-thione

A mixture of 5,6,7,8-tetrahydroquinazolin-4-one (3 g) and phosphorus pentasulphide (3 g) in pyridine (15 ml) was boiled under reflux for 1.5 h. It was cooled, diluted with water (40 ml), and evaporated. The residue dispersed in 95% ethanol was treated with charcoal to give, after partial removal of the solvent, the quinazolinethione (1.8 g, 54%), m.p. 281-282° (decomp.); concentration of the mother liquors gave more product (0.16 g, 5%); pK_a 1.95±0.05 (anal. λ 255 nm) and 8.13±0.04 (anal. λ 325 nm) (Found: C, 57.55; H, 6.1; N, 16.5; S, 19.5. $C_8H_{10}N_2S$ requires C, 57.8; H, 6.05; N, 16.85; S, 19.3%).

5,6,7,8-Tetrahydro-2-methylquinazoline-4(3*H*)-thione

This was made as the methylated homologue above but using 5,6,7,8-tetrahydro-2-methylquinazolin-4-one hydrochloride and boiling under reflux for 3 h. The reaction mixture after dilution with water and evaporation was triturated with water (5 ml). The solid was filtered off and well washed with cold water. The crude product in 95% ethanol was treated with charcoal and gave, by partial removal of the solvent, the quinazolinethione (64%), m.p. 239-240°; pK_a (20°) 2.35±0.05 (anal. λ 265 nm) and 8.91±0.02 (anal. λ 325 nm) (Found: C, 60.4; H, 6.4; N, 15.7; S, 17.5. $C_9H_{12}N_2S$ requires C, 60.0; H, 6.7; N, 15.55; S, 17.8%).

Potassium quinazoline-4-sulphonate

Quinazoline-4-thione (1 g) was oxidised with aqueous potassium permanganate as described for potassium 5-methylpyrimidine-2-sulphonate (p. 95). The potassium sulphonate (0.74 g, 48%), after crystallisation from ethanol-water (1:4) and drying at 25° *in vacuo*, had m.p. *ca* 326° (decomp.) (Found: C, 38.4; H, 1.9; N, 11.0; S, 12.7; K, 16.0. $C_8H_5KN_2O_3S$ requires C, 38.7; H, 2.0; N, 11.3; S, 12.9; K, 15.75%).

Potassium quinazoline-2-sulphonate

Similar oxidation of quinazoline-2-thione gave a material which could not be induced to crystallise from water, aqueous ethanol or aqueous acetone. It was purified partially by extraction with boiling anhydrous

methanol followed by evaporation. The crude material had the expected spectral properties and it was used to measure the approximate rate of hydrolysis.

Potassium 5,6,7,8-tetrahydroquinazoline-4-sulphonate

Similar oxidation of 5,6,7,8-tetrahydroquinazoline-4-thione (0.5 g) gave the sulphonate (0.35 g, 23%) which after drying at 120°/0.2 mmHg for 4 h had m.p. *ca* 332° (decomp.)(Found: C, 36.2; H, 3.3; N, 10.3; S, 12.2; K, 15.0. $C_8H_9KN_2O_3S$, $0.75H_2O$ requires C, 36.15; H, 4.0; N, 10.5; S, 12.1; K, 14.7%).

Potassium 5,6,7,8-tetrahydro-2-methylquinazoline-4-sulphonate

Similar oxidation of 5,6,7,8-tetrahydro-2-methylquinazoline-4-thione (0.5 g) gave the sulphonate (0.37 g, 21%), a sample of which decomposed *ca* 330° (Found: C, 38.35; H, 4.45; N, 9.6; S, 11.0; K, 13.7. $C_9H_{11}KN_2O_3S,H_2O$ requires C, 38.0; H, 4.6; N, 9.85; S, 11.3; K, 13.75%).

4-Hydrazinoquinazoline

Potassium quinazoline-4-sulphonate (100 mg) and hydrazine hydrate (0.5 ml) in 50% aqueous ethanol (2 ml) were boiled under reflux for 1 h. The resulting mixture was evaporated, diluted with water (10 ml), and extracted with chloroform. The residue from evaporation was sublimed to give the hydrazinoquinazoline (10 mg, 15%), M^+ = 160, shown by mass spectrometry to be contaminated

with quinazolin-4-one though apparently pure on t.l.c. (5% ammonia/ethanol). The compound after recrystallising twice from ethanol had m.p. 181-182° [Higashino, 1961: 188-189° (decomp.)] (Found: C, 59.7; H, 4.9; N, 34.45; M^+ 160. Calc. for $C_8H_8N_4$: C, 60.0; H, 5.0; N, 35.0%; M^+ 160).

Quinazoline-2-sulphonyl fluoride

Quinazoline-2-thione (0.81 g, 0.005 mol) was oxidised with chlorine in the presence of an excess of fluoride ion as for 5-methylpyrimidine-2-sulphonyl fluoride (p.103). The quinazolinesulphonyl fluoride (0.61 g, 58%), m.p. 103-104° (from methanol) had an extremely strong 'aromatic' smell (Found: C, 45.4; H, 2.7; N, 13.0; S, 14.6. $C_8H_5FN_2O_2S$ requires C, 45.3; H, 2.4; N, 13.2; S, 15.1%).

2-Diethylaminoquinazoline

Diethylamine (5 ml) was added to a sample of quinazoline-2-sulphonyl fluoride (the evaporated mother liquors from above). After the initial violent reaction the mixture was boiled under reflux for 10 min. The residue from evaporation was shown to be predominately one compound by t.l.c. (chloroform), not the starting material. Chromatography on alumina (chloroform) gave an oil which slowly crystallised. Treatment with ethanolic picric acid gave 2-diethylaminoquinazoline picrate, m.p. 210-211° (from ethanol) (Found: C, 50.0; H, 4.55; N, 19.25. $C_{18}H_{18}N_6O_7$ requires C, 50.2; H, 4.2; N, 19.5%).

The picrate in chloroform was chromatographed through alumina (Unilab: Brockmann activity 1, approx. neutral), eluting finally with chloroform-ethanol (3:1). Evaporation gave an oil which furnished (by molecular distillation at $90^{o}/15$ mmHg) 2-diethylaminoquinazoline, a strong smelling pale yellow oil (Found: N, 21.4; M^{+} 201. $C_{12}H_{15}N_3$ requires N, 20.9%; M^{+} 201).

Diquinazolin-2-yl disulphide

(1) Quinazoline-2-thione (0.1 g) in sodium bicarbonate solution (5 ml, pH *ca* 8.2) was titrated against a solution of iodine (0.3 g) in M-potassium iodide (10 ml) until the colour of the iodine persisted for 10-15 sec. The yellow colour of the thione faded during the titration. Filtration gave a crude product which was washed with dilute sodium bicarbonate and then dissolved in ethanol-chloroform and treated with charcoal. Evaporation and extraction of the solid with a little hot chloroform left a white residue of the disulphide, m.p. $256-257^{o}$ (Found: C, 54.0; H, 4.2; M^{+} 322. $C_{16}H_{10}N_4S_2,2H_2O$ requires C, 53.6; H, 3.95. Calc. for $C_{16}H_{10}N_4S_2$: M^{+} 322).

(2) A slurry of quinazoline-2-thione (0.25 g) in acetone (20 ml) was titrated against a solution of potassium permanganate (1 g) in acetone (60 ml) until a colouration persisted for 10-15 sec. Evaporation of the colourless filtrate gave a very small amount of yellow solid, shown to be the crude disulphide by mass spectrometry (M^{+} 322).

RATE MEASUREMENTS

The rates for alkaline, and in some cases acidic, hydrolysis of the potassium sulphonates, and the rates for the reaction of the pyrimidinesulphonyl fluorides with methanolic sodium methoxide were measured.

The slower alkaline hydrolyses were followed by a sampling technique. An approximately 2×10^{-4}M solution of each sulphonate (50 ml) in a 250 ml polypropylene flask sealed with a polyethylene-covered cork was preheated to the required temperature (generally 40°) and then diluted with an equal volume of similarly preheated sodium hydroxide solution (2.00M at 20°). Samples were removed at intervals from the thermostatted mixture and the optical density of each was measured immediately, at the predetermined analytical wavelength, with an SP500 spectrophotometer, against a 1.00M-sodium hydroxide blank. The time-lag (*ca* 15 sec) in this process proved insignificant. Because of the corrosive nature of these solutions care was taken that the same cells were used for each measurement and their orientation in the spectrophotometer was the same.

The faster alkaline hydrolyses, all the acid hydrolyses, and the reactions of the sulphonyl fluorides with sodium methoxide were followed by an admixture of an approximately 2×10^{-4}M solution of each sulphonate (in water), or sulphonyl fluoride (in methanol), with an equal

volume of 2.00M-sodium hydroxide, 5.70M-hydrochloric acid, or methanolic 0.103M-sodium methoxide, as appropriate, in a thermostatted all-Teflon stopped-flow rapid reaction apparatus (after Perrin, 1965) attached to a Shimadzu RS27 spectrophotometer recording optical density (at a predetermined wavelength) against time. The dissociation constants of the less stable species were similarly measured using this apparatus. Analytical wavelengths were established by superposition of the spectra of the initial and final species, generally by recording successive spectra during the course of the reaction. The analytical wavelength was chosen where the difference in absorption of the two species was maximal and at as high a wavelength as possible.

The rates for the alkaline hydrolyses at 40^{o} were corrected for the cubical expansion of water, which is effectively equivalent to a dilution of the reaction mixture; such corrections for the reactions at 25^{o} were insignificant. Reaction rates are expressed as first-order constants under defined conditions, rather than as second-order (pseudo first-order) constants, in order to avoid an inference of linear dependence of rate on molar concentration of acid or alkali in the H_0 and H^- regions examined. The k-values were calculated (see Appendix) by Guggenheim's method or from the general first-order rate equation: $k = 1/t \times \{\ln[a/(a-x)]\}$; those calculated by both methods were identical. Accuracy was confirmed

by a standard deviation of <3% or by a regression coefficient of > 0.9 (as appropriate) from *ca* 10 to *ca* 75% reaction.

The composition of the product of reaction was demonstrated either directly by purification from a more concentrated reaction mixture or by comparison of the final spectrum (after at least 5 x $t_{\frac{1}{2}}$) with that of the expected product.

APPENDIX

Calculation of the rates of reaction

The rates of reaction were calculated using a PDP8/I computor connected to a Hewlett Packard 7200A Graphic Plotter. Programs for the computations were written in FOCAL by the author.

a) Solution of the first order rate equation:-

The standard equation (1), modified for use with optical densities (2)(as measures of concentration) was

$$kt = \log[a/(a-x)] \qquad (1)$$

$$kt = \log[(D_\infty - D_0)/(D_\infty - D_x)] \qquad (2)$$

solved using the program A.1, which gave an output of the type A.2. Equation (2) implies a knowledge of the optical density of a reacting solution both at the start (t = 0) and at the finish [ideally $t > 10 \times t_{\frac{1}{2}}$ (99.9% reaction)] of the reaction. Experimentally it was difficult to measure either of these values as accurately as the intermediate values. Since every computation of the reaction rate (k) involves such initial and final measurements, errors in their measurement seriously affect the result (Guggenheim, 1926; Hammett, 1970). Random errors sometimes occurred and a statistical test was applied to the results to remove these. Any result with an error greater than 5 times the *probable error* was removed (Margenau and Murphy, 1943); the probable error was

```
*C-8K FOCAL @1969
*
*01.05 E
*01.06 C INPUT INITIAL AND FINAL VALUES OF OPTICAL DENSITY, AND
*01.07 C NUMBER OF OBSERVATIONS.
*01.10 A "DINIT",DI,"DINF",DN,"NO OF PTS",EN,!!
*01.40 T "  T        DOBS                K              %REACT",!
*01.45 C INPUT DATA PAIRS; TIME AND OPTICAL DENSITY.
*01.50 A T,"     ",DX
*01.55 C CALCULATE RATE CONSTANT.
*01.60 S Q=Q+1;S M=Q-EN;S Y=(DN-DI)/(DN-DX);S G=1/T
*01.80 S K=G*FLOG(Y);S KS(Q)=K;S L=L+K/EN
*
*02.10 T %,"       ",K,%4.02,"     ",%3.01,100*((DX-DI)/(DN-DI)),!
*02.20 I (M)1.5,3.1
*
*03.10 T !!,"AV. VALUE OF K ",%,L,'
*03.30 F I=1,EN;S SS=SS+KS(I)↑2
*03.40 S SD=FSQT((SS-EN*L↑2)/(EN-1))
*03.50 T %,"STD. DEVN.",SD,!,"          ( ",%4.02,SD*100/L,"% )"
*03.60 T !,"TIME FOR 50% REACT. ",%5.02,FLOG(2)/L,!!!
*
*05.01 C FIND RESIDUALS AND SORT (SECTIONS 6 AND 7)
*05.02 C IN ASCENDING VALUE.
*05.03 F Q=1,EN;S P(Q)=FABS(KS(Q)-L)
*05.04 F Q=1,EN-1;D 6
*05.06 F I=1,EN/2;S V=V+1;S W=W+P(I)
*05.07 C FIND PROBABLE ERROR.
*05.10 S W=0.8453*W/V
*05.15 C REJECT (SECTIONS 8 AND 9) UNACCEPTABLE VALUES AND
*05.16 C PRINTOUT REJECTS.
*05.20 F Q=1,EN;D 9;D 8
*05.30 S EN=X;S M=0;S SS=0
*05.35 F I=1,EN;S M=M+KS(I)
*05.38 C RETURN TO SECTION 3 AND RECALCULATE RESULTS.
*05.40 S L=M/EN;D 3
*05.90 Q
*
*06.10 S IS=Q;S XS=P(Q);S YS=KS(Q)
*06.20 F J=Q,EN;D 7
*06.30 S P(IS)=P(Q);S P(Q)=XS;S KS(IS)=KS(Q);S KS(Q)=YS
*
*07.10 I (P(J)-XS)7.2;R
*07.20 S XS=P(J);S IS=J;S YS=KS(J);R
*
*08.10 I (KS(Q))8.2,8.2;S X=X+1;S KS(X)=KS(Q)
*08.20 R
*
*09.05 I (5*W-P(Q))9.1,9.1,9.2
*09.10 T %,"BIN",KS(Q),!;S KS(Q)=0;R
*09.20 R
```

A.2

```
 G
DINIT:.Ø72 DINF:.752 NO OF PTS:8

  T        DOBS                  K                  %REACT
:Ø555      :.18Ø        Ø.3116284905E-Ø3              15.9
:Ø715      :.194        Ø.2765508165E-Ø3              17.9
:1465      :.298        Ø.2757649607E-Ø3              33.2
:165Ø      :.323        Ø.2791733004E-Ø3              36.9
:1895      :.349        Ø.2760719671E-Ø3              4Ø.7
:3105      :.462        Ø.2744643771E-Ø3              57.4
:349Ø      :.496        Ø.2799184567E-Ø3              62.4
:427Ø      :.54Ø        Ø.2729523655E-Ø3              68.8


AV. VALUE OF K  Ø.28Ø8155918E-Ø3
STD. DEVN. Ø.1265647299E-Ø4
          (   4.51% )
TIME FOR 5Ø% REACT.  2468.3


BIN Ø.3116284905E-Ø3


AV. VALUE OF K  Ø.2764137491E-Ø3
STD. DEVN. Ø.2457505991E-Ø5
          (   Ø.89% )
TIME FOR 5Ø% REACT.  25Ø7.6


*
```

obtained from an empirical weighting of the residuals [the modulus of the residuals from that half of the results with the smallest residuals were summed; this value, divided by the number summed, was taken as the *average error*; the *probable error* is 0.8543 times the average error (Margenau and Murphy, 1943)]. Calculation of rate constants by this method was unsatisfactory for most of the reactions studied; therefore, Guggenheim's method was generally used (see below). However because of the smaller demands on computor time (of program A.1 compared with program A.3) the method was used frequently to obtain preliminary results.

b) Guggenheim's method:-

Guggenheim (1926) devised a method for calculating the rate constant for a first-order reaction when the initial and final measures of the concentration were unknown. The program (A.3) used was constructed for spectrophotometric readings of optical density. It includes a correction for the cubical expansion of water. If a reasonable value for the initial optical density is known, the final value may be computed and hence the percentage of the total reaction studied may be calculated. The results are given as in A.4; in addition, the calculated results and the best straight line through these points (found by a linear regression) may be plotted (A.5). There was no provision for the removal of random errors; particularly bad results were obvious from the plotted output; and these were removed and the results recalculated.

C-8K FOCAL @1969

```
01.10 E
01.15 T !!,"ENTER NO OF PTS. THEN THE DATA TRIOS T V V'",!!;A N,!
01.40 F I=1,N;T %2,I,"    ";A T(I),V(I),V';S Y(I)=FLOG(V'-V(I));T !
01.44 T !,"ENTER CORRECTIONS  I  T  V  V'  ,END WITH I=0"
01.45 A !,I;I (I)1.6,1.6;A T(I),V(I),V';S Y(I)=FLOG(V'-V(I))
01.46 GOTO 1.45
01.50 C CALCULATE THE BEST STRAIGHT LINE THROUGH THE POINTS
01.51 C BY LINEAR REGRESSION.
01.60 F I=1,N;D 9
01.70 S D=S(1)*S(1)-N*S(4);S L=(S(1)*S(2)-N*S(3))/D
01.80 S B=(S(1)*S(3)-S(2)*S(4))/D
01.90 F I=1,N;S Z(I)=B+L*T(I)
01.92 F I=1,N;S S(6)=S(6)+(Z(I)-Y(I))↑2
01.93 S SD=(1/(FSQT(1+L↑2)))*FSQT(S(6)/N)
01.98 S Q=(N*S(4)-S(1)*S(1))*(N*S(5)-S(2)*S(2))
01.99 S R=(N*S(3)-S(1)*S(2))/FSQT(Q)

02.05 C CORRECT FOR CUBICAL EXPANSION OF WATER.
02.10 T !!;S K=-L;A "REACTION TEMP  ",RT,!!
02.20 S NO=1-.53255E-04*RT+.761532E-05*RT↑2-.437217E-07*RT↑3
02.24 S AA=NO+.164322E-09*RT↑4
02.28 S BB=1-.53255E-04*20+.76153E-05*20↑2
02.30 S CC=BB-.43721E-07*20↑3+.164322E-09*20↑4
02.35 S K=AA*K/CC
02.70 T !!"   RATE CONST.          ",%,K,!
02.87 T !"   REGRESSION COEFF.     ", %4.03, R
02.88 T !,"   STANDARD DEVN.       ",%,SD
02.89 T !!,%8.02,"TIME FOR 50% REACTION",FLOG(2)/K,"SECS."
02.90 T !!,"CALCN. OF DINF :ENTER VALUES OF DINIT UNTIL ACCEPTABLE"
02.91 T " DINF.",!," END WITH DINIT=-1",!!"   DINIT      DINF",!
02.92 S VI=0;A "    ",VO;I (VO)2.95,2.93,2.93
02.93 F I=1,N;S E=FEXP(L*T(I));S VI=VI+<(V(I)-VO*E)/(1-E)>/N
02.94 T %4.03,"    ",VI,!;GOTO 2.92
02.95 T !,"BEST VALUES  ";A "DINIT",VO,"DINF",VI
02.96 T !!,"REACTION FOLLOWED FROM ",%3.1,100*((V(1)-VO)/(VI-VO)),"%"
02.97 T " TO ",100*((V'-VO)/(VI-VO)),"%.",!!!
```

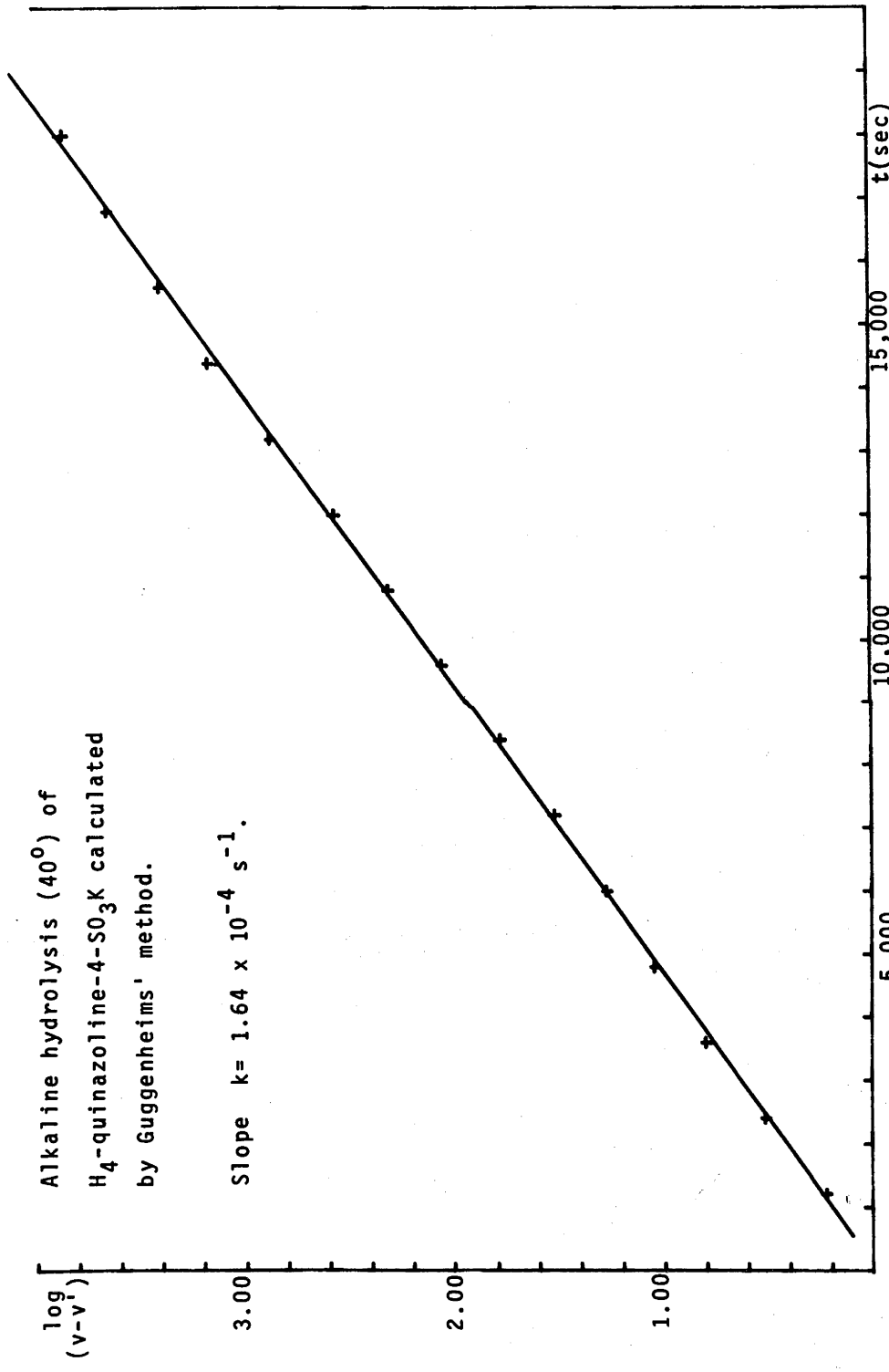
over →

```
Ø3.2Ø T !,"PLOT ROUTINE??, TYPE 1 FOR YES; ØFOR NO",!;A NN,!!!!!
Ø3.3Ø I (NN)4.6,4.6
Ø3.35 C TYPE ARRAYS OF INPUTTED DATA (FOR ESTM. OF PLOT LIMITS).
Ø3.4Ø T "     T(I)      Y(I)     Z(I)",!
Ø3.5Ø F I=1,N;T %7,T(I),"  ",%5.Ø3,Y(I),"  ",Z(I),!

Ø4.3Ø A "T MAX",ST,"  MOD. Y MAX",SY," MOD. Y MIN",YY,!
Ø4.31 S TB=9999/ST;S YB=9999/(SY-YY)
Ø4.5Ø F I=1,N;D 5
Ø4.55 D 8
Ø4.6Ø Q

Ø5.3Ø C PLOT POINTS (CROSS), AND CALCULATED VALUES (DOT).
Ø5.35 S TS=TB*T(I);S YS=YB*[FABS(Y(I))-YY]
Ø5.4Ø T "PLTL",!
Ø5.5Ø T %4,TS,YS-5Ø,!;T TS,YS+5Ø,!;T TS,YS,!
Ø5.6Ø T TS+4Ø,YS,!;T TS-4Ø,YS,!;T "PLTT",!
Ø5.7Ø S ZS=YB*[FABS(Z(I))-YY]
Ø5.71 T "PLTP",!
Ø5.72 T TS,ZS,!,TS,ZS,!;T "PLTT",!

Ø8.1Ø C FRAME.
Ø8.2Ø T "PLTL",!
Ø8.25 T %4,Ø,Ø,!,Ø,5ØØ,!
Ø8.3Ø F Y=499,5ØØ,9999;T X,Y,!,ØØ6Ø,Y,!,X,Y,!
Ø8.35 T "PLTT",!;T "PLTL",!;T ØØØØ,ØØØØ,!
Ø8.37 S Y=Ø
Ø8.4Ø F X=499,5ØØ,9499;T X,Y,!,X,Ø1ØØ,!,X,Y,!
Ø8.42 T X,Ø,!,X,1ØØØ,!
Ø8.45 F Y=999,1ØØØ,9999;T X,Y,!
Ø8.47 T "PLTT",!

Ø9.1Ø S S(1)=S(1)+T(I);S S(2)=S(2)+Y(I);S S(3)=S(3)+T(I)*Y(I)
Ø9.15 S S(4)=S(4)+T(I)*T(I);S S(5)=S(5)+Y(I)*Y(I)
*
```

A.4

```
 G

ENTER NO OF PTS. THEN THE DATA TRIOS T V V'

:15
  1    :1200 :.309 :.621
  2    :2400 :.371 :.6215
  3    :3600 :.420 :.622
  4    :4800 :.454 :.622
  5    :6000 :.481 :.6225
  6    :7200 :.505 :.623
  7    :8400 :.526 :.623
  8    :9600 :.544 :.6235
  9    :10800 :.558 :.6235
 10    :12000 :.570 :.624
 11    :13200 :.581 :.624
 12    :14400 :.590 :.6245
 13    :15600 :.596 :.625
 14    :16800 :.601 :.625
 15    :18000 :.605 :.6254

ENTER CORRECTIONS  I  T  V  V'  ,END WITH I=0
:15 :18000 :.605 :.6255
:0

REACTION TEMP  :40


   RATE CONST.          0.1637660856E-03

   REGRESSION COEFF.     -1.000
   STANDARD DEVN.       0.1980448530E-01

TIME FOR 50% REACTION   4232.54SECS.

CALCN. OF DINF :ENTER VALUES OF DINIT UNTIL ACCEPTABLE DINF.
 END WITH DINIT=-1

   DINIT       DINF
   :.220      0.644
   :.225      0.640
   :-1
BEST VALUES  DINIT:.220 DINF:.644

REACTION FOLLOWED FROM  21.0% TO  95.6%.
```

Plotting routine omitted


Alkaline hydrolysis (40°) of
H4-quinazoline-4-SO3K calculated
by Guggenheims' method.
Slope k= 1.64 x 10-4 s-1.
log (v-v')
3.00
2.00
1.00
5,000
10,000
15,000
t(sec)

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Simple Pyrimidines. Part XIII.[1] The Formation and Hydrolysis of Simple Potassium Pyrimidinesulphonates

By **D. J. Brown** * and **J. A. Hoskins**, Department of Medical Chemistry, John Curtin School of Medical Research, Canberra, Australia, 2600

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Simple Pyrimidines. Part XIII.[1] The Formation and Hydrolysis of Simple Potassium Pyrimidinesulphonates

By D. J. Brown * and J. A. Hoskins, Department of Medical Chemistry, John Curtin School of Medical Research, Canberra, Australia, 2600

Potassium 4-methyl-, 5-methyl-, 4,5-dimethyl-, and 4,6-dimethyl-pyrimidine-2-sulphonate, as well as potassium 2-methyl-, 4-methyl-, 2,4-dimethyl-, 4,5-dimethyl-, and 2,4,5-trimethyl-pyrimidine-6-sulphonate are prepared from appropriate chloropyrimidines with aqueous potassium sulphite. The sulphonates undergo ready hydrolysis to the corresponding pyrimidinones in alkali or acid: at pH 14 (40°) the $t_{\frac{1}{2}}$ values vary from 12 to 830 min and at H_0 −1 (25°) from 2 to 28 min, according to the position of the sulphonate group and the number and positions of the methyl groups (which retard hydrolysis). The pK_a values, characteristic i.r. bands, and u.v. spectra of the sulphonates are recorded and discussed; ^{1}H n.m.r. data are tabulated for the sulphonates, their chloro-intermediates, and their hydrolytic products.

DESPITE the implication of pyrimidine-(2, 4, or 6)-sulphonic acids as intermediates in the oxidative desulphurization of pyrimidinethiones,[2] few such acids have been isolated even as their salts. Ochiai and Yamanaka[3] succeeded in characterizing sodium 2,4-dimethylpyrimidine-6-sulphonate (1); the remaining examples have at least one powerfully electron-releasing substituent.[4] We now report the formation of a series of nine simple *C*-methylated potassium pyrimidinesulphonates (listed in Table 1); their ionization constants and spectra; and the rates of their ready hydrolysis to the corresponding pyrimidinones in alkali or acid.

TABLE 1

Rates of hydrolysis

Pyrimidine	Temp.[a] (°C)	Anal. λ (nm)	$k \times 10^5$ [b,c] (s^{-1})	$t_{\frac{1}{2}}$ [c] (min)
2-Sulphonic acids				
Unsubst.	40	292	93·9 (93)	12·3
	25	292	26·1 (77)	44·2
4-Me	40	288	27·5 (96)	42·0
	25	290	8·34 (82)	139
	25	302	*139* (92)	*8·35*
5-Me	40	304	5·26 (91)	220
4,5-Me_2	40	300	1·40 (94)	828
4,6-Me_2	40	288	8·83 (92)	131
	25	315	*359* (75)	*3·23*
6-Sulphonic acids				
2-Me	40	273	98·8 (97)	11·7
	25	273	30·3 (87)	38·2
	25	273	*547* (79)	*2·12*
4-Me	40	273	58·0 (98)	19·9
	25	230	*109* (70)	*10·6*
2,4-Me_2	40	273	21·6 (96)	53·5
	25	230	*120* (74)	*9·63*
4,5-Me_2	40	273	4·63 (92)	249
	25	238	*41·3* (63)	*28·0*
2,4,5-Me_3	40	232	1·90 (79)	609
	25	237	*87·5* (85)	*13·2*

[a] Thermostatted to ±0·1°. [b] Reaction followed from <10% to % in parentheses. [c] Values in Roman type refer to alkaline hydrolysis (1·00M-sodium hydroxide); those in italics, to acidic hydrolysis (2·85M-hydrochloric acid).

The pyrimidinesulphonates were prepared by boiling the corresponding chloropyrimidines in aqueous potassium sulphite for the minimum time consistent with complete displacement of each chloro-substituent; longer reaction times caused progressive hydrolysis of the product, as did also any variation from an optimum initial pH of 7. The choice of potassium sulphite was dictated by experiments with several metal sulphites: the potassium pyrimidinesulphonates proved least troublesome to separate from inorganic chlorides and sulphites in the reaction mixtures. Even so, several such sulphonates could not be separated from non-stoicheiometric proportions of potassium chloride: repeated recrystallization or variation within the limited range of useful solvents effected no improvement, often the reverse. The chloro-intermediates were prepared by established methods (see Experimental section) from the corresponding pyrimidinones, one of which was made by a greatly improved route: the readily available[5] 4-chloro-2-methylpyrimidin-6-one (2; R = Cl) was converted into the mercapto-analogue (2; R = SH) which was desulphurized with Raney nickel to give the required pyrimidinone (2; R = H) in >80% yield; this route avoided the primary synthesis[6] (<20% yield) from acetamidine and crude ethyl sodioformylacetate (which contains *ca.* 33% ethyl sodioacetoacetate[7]) followed by purification of the product from the by-product, 2,4-dimethylpyrimidin-6-one (2; R = Me).

Preliminary experiments revealed that the sulphonates were reasonably stable as anions at pH 7 but that they hydrolysed rapidly (as anions) in strong alkali, or as neutral molecules or zwitterions in strongly acidic solution, to give the corresponding pyrimidinones. One of these products (2; R = Me) was isolated for identification with authentic material; identities of other pyrimidinones were checked by comparing the u.v. spectra of their solutions with those of the corresponding authentic specimens under comparable conditions, and in some cases by their ^{1}H n.m.r. spectra (Table 4). The above hydrolyses were then followed spectrometrically at pH

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[4] D. J. Brown, 'The Pyrimidines' and 'The Pyrimidines Supplement I,' Wiley, New York, 1962 and 1970 respectively.
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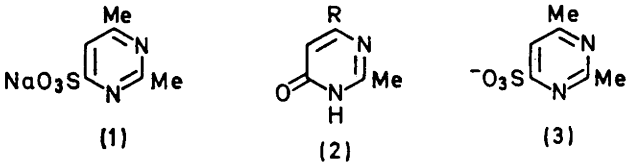
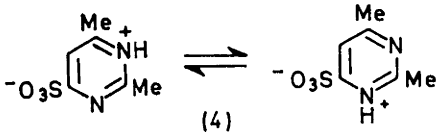
[7] M. Cogon, *Bull. Soc. chim. France*, 1941, 125.

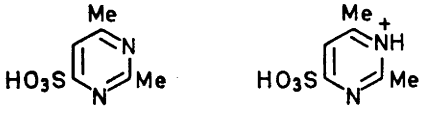
14·0 and (after determination of the pK_a values for gain of a proton by the anions; see below) at H_0 −1 where the 6-sulphonates all contained <5% anion and at least one of the 2-sulphonates contained <10% anion; a lower H_0 value was impractical for use in the available



(1) (2) (3)



(4)



(5) (6)

rapid-reaction apparatus because of the exothermic nature of the dilutions involved. Comparing alkaline hydrolyses at 40° (Table 1), the 4-sulphonates were 2—3 times more reactive than their 2-isomers and the deactivating effect of each added methyl group was considerable: each 2-, 4-, or 6-methyl group decreased the rate by a factor of 3—4; a 5-methyl group by a factor of 12—20. Repetition of some of the hydrolyses at 25° indicated that the rates doubled approximately for a 10° rise. On the available data for acidic hydrolyses at 25°, differences between 2- and 6-sulphonic acids were rather less marked than above; so too was the effect of each methyl group, especially at the 5-position; in addition, anomalies occurred: 2,4-dimethyl- reacted more rapidly than 4-methyl-, and 2,4,5-trimethyl- more rapidly than 4,5-dimethyl-pyrimidine-6-sulphonic acid.

Within an H_0 range limited by the progressive instability of the sulphonic acids and by the rapid-reaction apparatus itself, only one pK_a emerged from each acid using the spectrometric method. Clearly each such value represented the addition of a proton to the sulphonate anion, *e.g.* (3), to give the zwitterion (4) rather than the neutral species (5) because the change was accompanied by a small bathochromic shift and an increase in absorption at $\lambda_{max.}$ (Table 2), a phenomenon typical of *N*-protonation of the pyrimidine ring [8] and parallel to the behaviour of pyridinesulphonic acids.[9] Moreover, had protonation occurred at the sulphonate group little, if any, spectral change would be expected, a postulate confirmed by the lack of appreciable change [10] in the spectrum of toluenesulphonic acid (pK_a −1·1 [11] or −1·3 [12]; *cf.* methanesulphonic acid: [13] −1·2) from pH 7 to H_0 −5; likewise, any further protonation, *e.g.* (4) ⟶ (6), should be spectrally invisible.

TABLE 2

Ionization and u.v. spectra

Pyrimidine	pK_a' [a]	$\lambda_{max.}$ (log ε) [b]
2-Sulphonic acids		
Unsubst.	−1·70 ± 0·07 (250)	246 (—) [c]
4-Me	−0·76 ± 0·07 (252)	248 (3·43)
5-Me	−1·21 ± 0·06 (265)	253 (3·43)
4,5-Me$_2$ [d]	−0·33 ± 0·04 (265)	253 (3·56)
4,6-Me$_2$	−0·09 ± 0·04 (255)	248 (3·50)
6-Sulphonic acids		
2-Me	0·78 ± 0·04 (260)	256 (3·71), *262 (3·60)*
4-Me	0·23 ± 0·04 (262)	252 (3·65)
2,4-Me$_2$	1·62 ± 0·04 (270) [e]	257 (3·55); 263 (3·56)
4,5-Me$_2$	1·20 ± 0·04 (275) [e]	260 (3·74); 266 (3·88) [f]
2,4,5-Me$_3$	2·33 ± 0·04 (276) [e]	264 (3·72); 269 (3·84) [f]

[a] Addition of proton to nitrogen atom of anion at 25°. [b] Aqueous solution of potassium salt; where necessary, allowance made for associated potassium chloride in recording log ε. [c] Crude material. [d] Hydrolysis gave 4,5-dimethylpyrimidin-2-one, pK_a 3·37 ± 0·02 (analyt. λ 317 nm). [e] At 20°. [f] Zwitterion at H_0 −1.

The pK_a values in Table 2 indicate an appreciable increase with each added *C*-methyl group although the extent depends on position: with a single exception, ΔpK_a is 1·1—1·4 (2-Me), 0·7—1·0 (4- or 6-Me), and 0·4—0·7 (5-Me). Such positional dependance is seen in terms of the two ways [9,14] [inductive (+*I*) and hyperconjugative (+*M*)] in which a methyl group can affect the ease of protonation at each ring-nitrogen atom. Thus a 2-methyl group has a double effect on both these potential sites for protonation; a 4-methyl group has a double effect on one site but only a single effect on the other; and a 5-methyl group has only a single diminished (inductive) effect on both sites. The above ΔpK_a values may be used to predict a pK_a of *ca.* −0·4 for pyrimidine-4-sulphonic acid which we were unable to prepare because of the instability of 4-chloropyrimidine in aqueous media.

The i.r. spectra of sulphonic acids and their salts have not been investigated widely. However it is clear [15] that vibrations of the sulphonate group are manifest in two regions, 1230—1120 and 1080—1025 cm^{-1}; in particular, aromatic sulphonates [16] often have bands at or near 1230, 1190, 1130, and 1040 cm^{-1}, representing the interaction of three SO and one SC vibrations. In the zwitterionic [9] pyridine-2-sulphonic acid we have observed bands at closely similar frequencies (Table 3) but

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[16] N. B. Colthup, L. H. Daly, and S. E. Wiberly, 'Raman and Infra-red Spectroscopy,' Academic Press, New York, 1964.

TABLE 3

Characteristic i.r. bands of sulphonates

Compound	Region A (cm^{-1})	Region B
Pyridine-2-SO_3H	1237, 1198, 1138	1032
Pyrimidine-2-SO_3K	1250, 1200	1032
4-Me	1251, 1232, 1203	1048
5-Me	1215	1034
4,5-Me_2	1245, 1220	1052
4,6-Me_2	1244, 1214	1062
Pyrimidine-6-SO_3K	—	—
2-Me	1255, 1198	1045
4-Me	1215	1048
2,4-Me_2	1254, 1232, 1210	1068
4,5-Me_2	1250, 1238, 1202	1029
2,4,5-Me_3	1202	(1055, 1030, 1015) [a]

[a] Partially resolved.

TABLE 4

^1H N.m.r. spectra

Pyrimidine [a]	δ [b]
2-SO_3K (*A*)	5-H: 7·76 (t, *J* 6); 4-H and 6-H: 9·3 (d, *J* 6)
4-Me-2-SO_3K (*A*)	Me: 2·61; 5-H: 7·61 (d, *J* 5·1); 6-H: 8·82 (d, *J* 5·1)
5-Me-2-SO_3K (*A*)	Me: 2·36; 4-H and 6-H: 8·77
4,5-Me_2-2-SO_3K (*A*)	5-Me: 2·34; 4-Me: 2·56; 6-H: 8·58
4,6-Me_2-2-SO_3K (*A*)	4-Me and 6-Me: 2·54; 5-H: 7·45
2-Me-6-SO_3K (*A*)	Me: 2·82; 5-H: 7·99 (d, *J* 6); 4-H: 9·16 (d, *J* 6)
4-Me-6-SO_3K (*A*)	Me: 2·65; 5-H: 7·94 (d, *J* 1); 2-H: 9·18 (d, *J* 1)
2,4-Me_2-6-SO_3K (*A*)	4-Me: 2·64; 2-Me: 2·75; 5-H: 7·76
(*B*) [c]	4-Me: 2·83; 2-Me: 2·92; 5-H: 8·17
4,5-Me_2-6-SO_3K (*A*)	4-Me and 5-Me: 2·58; 2-H: 8·94
(*B*) [c]	5-Me: 2·73; 4-Me: 2·91; 2-H: 9·42
2,4,5-Me_3-6-SO_3K (*A*)	4-Me and 5-Me: 2·53; 2-Me: 2·65
2-Cl-4-Me (*C*)	Me: 2·50; 5-H: 7·11 (d, *J* 5·5); 6-H: 8·47 (d, *J* 5·5)
2-Cl-5-Me (*C*)	Me: 2·32; 4-H and 6-H: 8·38
2-Cl-4,5-Me_2 (*D*)	5-Me: 2·32; 4-Me: 2·47; 6-H: 8·41
4-Cl-2-Me (*E*)	Me: 2·78; 5-H: 7·35 (d, *J* 4); 6-H: 8·76 (d, *J* 4)
4-Cl-2,5,6-Me_3 (*C*)	5-Me: 2·29; 6-Me: 2·44; 2-Me: 2·55
2,4-Cl_2-6-Me (*C*)	Me: 2·50; 5-H: 7·20
2,4,6-Cl_3-5-Me (*C*)	Me: 2·50
4-Cl-6-OH-5-Me (*E*)	Me: 2·21; 2-H: 8·13
4-OH-2-Me (*A*)	Me: 2·64; 5-H: 6·64 (d, *J* 7); 6-H: 8·17 (d, *J* 7)
4-OH-6-Me (*B*)	Me: 2·48 (d, *J* 1); 5-H: 6·66 (m) [d]; 2-H: 9·28 (m) [d]
2-OH-4,5-Me_2 (*B*)	5-Me: 2·24; 4-Me: 2·69 [e]; 6-H: 8·54
2-OH-4,6-Me_2 (*B*)	4-Me and 6-Me: 2·64; 5-H: 6·85
4-OH-2,6-Me_2 (*A*)	6-Me: 2·26; 2-Me: 2·42; 5-H: 6·20
(*B*) [c]	6-Me: 2·44; 2-Me: 2·74 [e]; 5-H: 6·53
4-OH-5,6-Me_2 (*B*)	5-Me: 2·13; 6-Me: 2·51; 2-H: 9·23

[a] Solvents: *A* = D_2O, *B* = M-DCl in D_2O, *C* = CCl_4, *D* = no solvent, *E* = $CDCl_3$; pyrimidinones designated as hydroxypyrimidines for convenience. [b] Singlet peaks unless indicated otherwise; *J* in Hz; Me_4Si or $Me_3Si[CH_2]_3SO_3Na$ as internal standard. [c] Methyl assignments tentative. [d] Poorly resolved. [e] Slowly disappears by deuteriation; *cf.* T. J. Batterham, D. J. Brown, and M. N. Paddon-Row, *J. Chem. Soc.* (*B*), 1967, 171.

the spectra of the pyrimidinesulphonates are less simple: each shows a strong, broad, and complex band at 1250—1200 cm^{-1} in which up to three small partially resolved peaks may be visible (region A) and a strong sharp band at 1070—1015 cm^{-1} (region B).

Besides their use in confirming the structures of chloro-intermediates, sulphonates, and hydrolytic products (Table 4), ^1H n.m.r. spectra helped to detect and identify any gross organic impurities in the crude sulphonates, *e.g.* the pyrimidin-2-one which could not be removed from potassium pyrimidine-2-sulphonate.

EXPERIMENTAL

Analyses were done by Dr. J. E. Fildes and her staff. ^1H N.m.r. spectra were measured at 60 MHz and 33° by Mr. S. E. Brown; u.v. spectra were recorded with an SP 800 spectrophotometer and peaks were checked with an SP 500 manual instrument; i.r. spectra (Nujol mull) were recorded with an SP 200 spectrophotometer. Ionization constants were measured spectrometrically at concentrations below 10^{-3}M, where possible in buffers [17] of 10^{-2}M ionic strength. For unstable sulphonates of low pK_a, a stopped-flow rapid reaction technique [18] (if necessary, in conjunction with an extrapolation procedure [19] to avoid the exothermic dilution of concentrated acids) was used.

Potassium Pyrimidinesulphonates.—4-Chloro-2,6-dimethylpyrimidine [20] (1·45 g, 0·01 mol) was added to a solution of freshly prepared potassium sulphite dihydrate (see below; 1·94 g, 0·01 mol) in water (10 ml), preadjusted (if necessary) to pH 7 by the addition of potassium carbonate. The mixture was boiled under reflux for 20 min and then evaporated. The residue was dehydrated by admixture with chloroform (10 ml) and subsequent distillation. Extraction by boiling anhydrous methanol (3 × 10 ml) and evaporation of the extracts gave *potassium 2,4-dimethylpyrimidine-6-sulphonate* (>70%), m.p. *ca.* 326° (decomp.) after recrystallization from aqueous ethanol and drying at 80°/0·1 mmHg (Found: C, 31·9; H, 3·4; K, 17·1; S, 14·4. $C_6H_7KN_2O_3S$ requires C, 31·8; H, 3·1; K, 17·3; S, 14·15%).

A similar method (optimum reflux time given) was used to convert 2-chloro-4,6-dimethylpyrimidine [21] into *potassium 4,6-dimethylpyrimidine-2-sulphonate* (2 h; 51%), m.p. 292—293° (decomp.) (Found: C, 31·45; H, 3·0; K, 16·9; N, 12·35; S, 14·05. $C_6H_7KN_2O_3S$ requires C, 31·8; H, 3·1; K, 17·3; N, 12·4; S, 14·15%); 4-chloro-5,6-dimethylpyrimidine [22] into *potassium 4,5-dimethylpyrimidine-6-sulphonate* (1 h), m.p. 331° (decomp.) (Found: C, 32·3; H, 3·05; K, 17·0; N, 12·2; S, 14·1. $C_6H_7KN_2O_3S$ requires C, 31·8; H, 3·1; K, 17·3; N, 12·4; S, 14·15%); 2-chloro-4,5-dimethylpyrimidine [23] into *potassium 4,5-dimethylpyrimidine-2-sulphonate* (5 h; 74%); m.p. 314° (decomp.) (Found: K, 17·3; S, 14·05. $C_6H_7KN_2O_3S$ requires K, 17·3; S, 14·15%); 2-chloro-4-methylpyrimidine [24] into *potassium 4-methylpyrimidine-2-sulphonate* (40 min), m.p. 290—295° (decomp.) (Found: K, 18·2; S, 15·1. $C_5H_5KN_2O_3S$ requires K, 18·4; S, 15·1%).

The following sulphonates were prepared similarly

[17] D. D. Perrin, *Austral. J. Chem.*, 1963, **16**, 572.
[18] D. D. Perrin, *Adv. Heterocyclic Chem.*, 1965, **4**, 43.
[19] A. Albert and E. P. Serjeant, 'Ionization Constants of Acids and Bases,' Methuen, London, 1962, p. 84 *et seq.*
[20] K. F. M. J. Schmidt, *Ber.*, 1902, **35**, 1575; M. P. L. Caton, D. T. Hurst, J. F. W. McOmie, and R. R. Hunt, *J. Chem. Soc.* (*C*), 1967, 1204.
[21] G. M. Kosolapoff and C. H. Roy, *J. Org. Chem.*, 1961, **26**, 1895.
[22] R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman, and A. R. Todd, *J. Chem. Soc.*, 1946, 361.
[23] S. Sugasawa, S. Yamada, and M. Narabashi, *J. Pharm. Soc. Japan*, 1951, **71**, 1345.
[24] J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1951, 1014.

(reference to chloro-precursors given) but could not be separated from associated potassium chloride. Specimens with the compositions given below showed no sign of organic impurities (t.l.c. on silica with 10% ethanol in chloroform; u.v., i.r., and ^{1}H n.m.r. spectra) and were used for hydrolysis-rate and log ε measurements: *potassium 2,4,5-trimethylpyrimidine-6-sulphonate* [22] (Found: K, 17·35; N, 11·05; S, 13·1. $C_7H_9KN_2O_3S$ + 3% KCl requires K, 17·35; N, 11·3; S, 12·95%); *potassium 4-methylpyrimidine-6-sulphonate* [24] (Found: C, 23·0; H, 2·0; N, 10·6; S, 11·95. $C_5H_5KN_2O_3S$ + 20·2% KCl requires C, 22·6; H, 1·9; N, 10·5; S, 12·05%); *potassium 5-methylpyrimidine-2-sulphonate* [25] (Found: C, 26·75; H, 2·5; N, 12·7; S, 14·3. $C_5H_5KN_2O_3S$ + 5% KCl requires C, 26·85; H, 2·3; N, 12·5; S, 14·35%); *potassium 2-methylpyrimidine-4-sulphonate* (from 4-chloro-2-methylpyrimidine: see below) (Found: C, 25·6; H, 2·05; N, 11·6; S, 13·7. $C_5H_5KN_2O_3S$ + 9·5% KCl requires C, 25·6; H, 2·15; N, 11·9; S, 13·7%). Crude potassium pyrimidine-2-sulphonate was prepared from 2-chloropyrimidine: the best specimen contained *ca.* 9% 2-hydroxypyrimidine (as revealed by t.l.c. and u.v. absorption at 296 nm) as well as potassium chloride.

Hydrolyses of Potassium 2,4-Dimethylpyrimidine-6-sulphonate.—The salt (0·25 g) was added to 2·85N-hydrochloric acid (20 ml). After 18 h at 25° the mixture was adjusted to pH 6 and evaporated. The dry residue was continuously extracted with ethyl acetate. Removal of the solvent and recrystallization from ethanol gave 2,4-dimethylpyrimidin-6-one (80%), identified by i.r. spectroscopy and mixed m.p. (199—200°) with authentic material.[26] Similar treatment of the sulphonate in N-sodium hydroxide at 40° gave an identical product (66%).

Pyridine-2-sulphonic Acid.—In the oxidation [27] of pyridine-2-thione, it was found essential to use brown rather than colourless nitric acid. The sulphonic acid (from ethanol) had m.p. 256° (lit.,[27] 251—252°).

4-Chloro-2-methylpyrimidine.—Hydrogen sulphide was passed into a stirred mixture of 4-chloro-2-methylpyrimidin-6-one [5] (2·9 g), sodium hydrogen sulphide (commercial; 2·0 g), and 2-ethoxyethanol (20 ml), first for 10 min at 25° and subsequently for 60 min while boiling under reflux. The cooled solution, adjusted to pH 2 with 5N-hydrochloric acid, gave 4-mercapto-2-methylpyrimidin-6-one [28] (91%), m.p. 301° (decomp.). This crude material (2·0 g) was dissolved in N-ammonia and boiled under reflux with Raney nickel (6 g, weighed wet) for 45 min. The filtered solution was evaporated to give 2-methylpyrimidin-4-one (93%), m.p. 213° after sublimation at 115°/0·2 mmHg (lit.,[29] 213°) and pK_a (20°): 2·73 ± 0·04 (anal. λ 290 nm) (Found: C, 54·5; H, 5·5; N, 25·45. Calc. for $C_5H_6N_2O$: C, 54·5; H, 5·4; N, 25·55%). This was converted by Gabriel's method [29] into the 4-chloro-analogue (65%), m.p. 59—60° (after sublimation at 35°/1·0 mmHg) (Found: Cl, 27·8. Calc. for $C_5H_5ClN_2$: Cl, 27·6%).

Potassium Sulphite Dihydrate.—Commercial material proved unsatisfactory for the above preparations. Accordingly, sulphur dioxide was passed into a stirred mixture of potassium carbonate (50 g) and water (50 ml) until the supernatant liquid reached pH 6. After cooling in ice, the solid was filtered off and well pressed. It was dried *in vacuo* over calcium chloride and stored in an air-tight bottle. The shelf-life was less than 3 months at 25°.

Rate Measurements.—The slower alkaline hydrolyses were followed by a sampling technique. An approximately 2×10^{-4}M-solution of each sulphonate in a polypropylene flask sealed with a Polythene-covered cork was preheated to the required temperature and then diluted with an equal volume of similarly preheated sodium hydroxide solution (2·00M at 25°). Samples were removed at intervals from the thermostatted mixture and the optical density of each was measured immediately at the predetermined analytical wavelength with an SP 500 spectrophotometer. The time-lag (*ca* 15 s) in this process proved insignificant.

The faster alkaline and all the acid hydrolyses were followed by admixture of an approximately 2×10^{-4}M solution of each sulphonate with an equal volume of 2·00M-sodium hydroxide or 5·70M-hydrochloric acid in a thermostatted all-Teflon stopped-flow rapid-reaction apparatus [18] attached to a Shimadzu RS27 spectrophotometer recording optical density (at a predetermined wavelength) against time.

Reaction rates are expressed as first-order constants under defined conditions, rather than second-order (pseudo first-order) constants, in order to avoid an inference of linear dependence of rate on molar concentration of acid or alkali in the H_0 and H^- regions examined. The k-values were calculated by Guggenheim's method [30] or from the general first-order rate equation: $k = 1/t \times \ln [a/(a - x)]$; those calculated by both methods were identical. Accuracy was confirmed by a standard deviation of <3% or by a regression coefficient of >0·9 (as appropriate) from <10 to *ca.* 75% reaction.

We thank Professor A. Albert, Dr. D. D. Perrin, and Dr. T. J. Batterham for discussions; Dr. D. A. Buckingham for the loan of a rapid-reaction apparatus; and the Australian National University for supporting J. A. H. as a Scholar.

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Simple Pyrimidines. Part XIV.[1] The Formation and Reactions of Some Derivatives of Simple Pyrimidinesulphonic Acids

By **D. J. Brown** * and **J. A. Hoskins**, Department of Medical Chemistry, John Curtin School of Medical Research, P.O. Box 334, Canberra City, Australia 2601

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Simple Pyrimidines. Part XIV.[1] The Formation and Reactions of Some Derivatives of Simple Pyrimidinesulphonic Acids

By **D. J. Brown** * and **J. A. Hoskins**, Department of Medical Chemistry, John Curtin School of Medical Research, P.O. Box 334, Canberra City, Australia 2601

Appropriate pyrimidine-2-thiones react with chlorine in the presence of potassium hydrogen difluoride to give pyrimidine-2-sulphonyl fluoride (2; R = H, X = F) and its 4-methyl, 5-methyl, and 4,6-dimethyl derivatives. Under mild conditions, these react with ammonia to give the corresponding sulphonamides and with amines to give, for example, *N*(2)-ethyl-4,6-dimethylpyrimidine-2-sulphonamide (2; R = Me, X = NHEt); also the analogous *NN*-diethyl-sulphonamide, 2-sulphonomorpholide, *NN*-di-isopropylsulphonamide, and sulphonohydrazide (converted into its *N*-isopropylidene derivative). Under more vigorous conditions, the whole sulphur-containing group is displaced to yield, for example, 2-hydrazino-, 2-diethylamino-, 2-azido-, and 2-methoxy-4,6-dimethylpyrimidine; also 2-hydrazino- and 2-azido-5-methylpyrimidine. The reaction rate for each sulphonyl fluoride with methoxide ion depends on the number and position of the *C*-methyl substituents. 4,6-Dimethylpyrimidine-2-thione (1; R = Me) is oxidized by chloramine to a separable mixture of the corresponding sulphenamide (3; R = S·NH_2) and disulphide; and by aqueous permanganate to the potassium sulphonate. This latter improved method also yields potassium 5-methylpyrimidine-2-sulphonate and the isomeric 4-methylpyrimidine-6-sulphonate. Appropriate sulphonates and sulphonamides react with hydrazine to give 2-hydrazino-4,6- and 4-hydrazino-2,6-dimethylpyrimidine (4). U.v. and ^{1}H n.m.r. spectra were used to confirm structures and to follow reactions.

APART from some pioneering work in connection with carbonic anhydrase inhibitors,[2] derivatives of simple pyrimidinesulphonic acids (lacking other functional substituents) have been neglected.[3] We now describe the preparation of some simple pyrimidine-2-sulphonyl fluorides and their conversion into sulphonamides and sulphonohydrazides; an improved method (*cf.* ref. 1) for making potassium pyrimidinesulphonates, involving

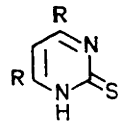
[1] Part XIII, D. J. Brown and J. A. Hoskins, *J. Chem. Soc.* (*B*), 1971, 2214.

[2] R. O. Roblin and J. W. Clapp, *J. Amer. Chem. Soc.*, 1950, **72**, 4890.

[3] D. J. Brown, 'The Pyrimidines,' Wiley, New York, 1962, p. 295 *et seq.*; 'The Pyrimidines: Supplement I,' 1970, p. 221 *et seq.*

oxidation of pyrimidinethiones; the displacement of such S^{VI}-groups by appropriate nucleophiles to give the corresponding amino-, hydrazino-, azido-, hydroxy-, and methoxy-pyrimidines; and the formation of a simple pyrimidinesulphenamide and some hitherto unknown disulphides.

The experience of Beaman and Robins [4] in the purine series suggested that simple pyrimidinesulphonyl fluorides might prove to be more amenable than the corresponding chlorides, which were known [2] to be highly unstable. Accordingly, a well cooled solution of the pyrimidinethione (1; R = Me) containing potassium hydrogen difluoride was treated with a stream of chlorine. The sulphonyl fluoride (2; R = Me, X = F) which resulted in good yield, was a low-melting solid,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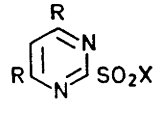
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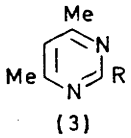
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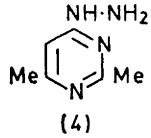
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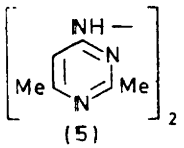
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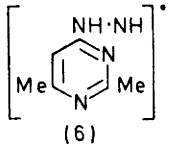
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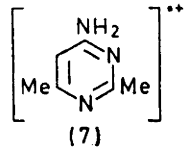
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stable to recrystallization from boiling ethanol, and had not decomposed after a year. Other thiones were oxidized similarly to give, for example, pyrimidine-2-sulphonyl fluoride (2; R = H, X = F) and its 4- and 5-methyl derivatives, but attempts to prepare 2,4-dimethylpyrimidine-6-sulphonyl fluoride by this method failed on account of the instability of the product. The ^{1}H n.m.r. and u.v. spectra of the sulphonyl fluorides and some derived or related pyrimidines are given in Tables 1 and 2; characteristic i.r. absorptions are recorded in the Experimental section.

On dissolution in liquid ammonia, the sulphonyl fluoride (2; R = Me, X = F) was converted rapidly into the sulphonamide (2; R = Me, X = NH_2), identical with a specimen prepared by modification of the known [2] procedure; pyrimidine-2-sulphonamide (2; R = H, X = NH_2) and its 4- and 5-methyl derivatives were made similarly. The fluoride (2; R = Me, X = F) also reacted under mild conditions with appropriate amines to give the *N*(2)-substituted 4,6-dimethylpyrimidine-2-sulphonamides [2; R = Me; X = NHEt, NEt_2, NPr^i_2, $N(CH_2{\cdot}CH_2)_2O$, or $NH{\cdot}NH_2$]; the last of these was characterized additionally as its isopropylidene derivative (2; R = Me, X = $NH{\cdot}N{:}CMe_2$). Under more vigorous conditions, the whole 2-substituent of 5-methylpyrimidine-2-sulphonyl fluoride or of the pyrimidines (2; R = Me, X = F, NH_2, or $NH{\cdot}NH_2$) underwent nucleophilic displacement by amines to give,

[4] A. G. Beaman and R. K. Robins, *J. Amer. Chem. Soc.*, 1961, **83**, 4038.

TABLE 1

^{1}H N.m.r. spectra

Pyrimidine [a]	δ [b]
2-SO_2F (A)	5-H: 7·85(t, *J* 5); 4-H and 6-H: 9·20 (d, *J* 5)
2-SO_2F-4-Me (A)	4-Me: 2·76; 5-H: 7·78 (d, *J* 5); 6-H: 8·99 (d, *J* 5)
2-SO_2F-5-Me (A)	5-Me: 2·60; 4-H and 6-H: 8·99
2-SO_2F-4,6-Me_2 (B)	4-Me and 6-Me: 2·61; 5-H: 7·85
2-$SO_2{\cdot}NH_2$-4-Me (C)	4-Me: 2·80; 5-H: 7·87 (d, *J* 6); 6-H: 9·05 (d, *J* 6)
2-$SO_2{\cdot}NH_2$-4,6-Me_2 (B)	4-Me and 6-Me: 2·54; 5-H: 7·53
2-$SO_2{\cdot}NHEt$-4,6-Me_2 (A)	Et: 1·20 (t, *J* 7), 3·35 (q, *J* 7); 4-Me and 6-Me: 2·60; NH: 4·96br (t, *J ca.* 6); 5-H: 7·25
2-$SO_2{\cdot}NEt_2$-4,6-Me_2 (A)	Et: 1·20 (t, *J* 7), 3·48 (q, *J* 7); 4-Me and 6-Me: 2·58; 5-H: 7·24
2-$SO_2{\cdot}NPr^i_2$-4,6-Me_2 (C)	Pr^i: 1·34 (d, *J* 6·8), 3·61 (m); 4-Me and 6-Me: 2·62; 5-H: 7·75
2-$SO_2{\cdot}NH{\cdot}NH_2$-4,6-Me_2 (A)	4-Me and 6-Me: 2·61; NH_2: *ca.* 3·9br; 5-H: 7·28
2-$SO_2{\cdot}NH{\cdot}N{:}CMe_2$-4,6-$Me_2$ (A)	CMe_2: 1·93; 4-Me and 6-Me: 2·56; 5-H: 7·22
2-$NH{\cdot}NH_2$-5-Me (A)	5-Me: 2·21; NH_2: 4·0br; NH: 6·95br; 4-H and 6-H: 8·51
4-$NH{\cdot}NH_2$-2,6-Me_2 (C)	2-Me and 6-Me: 2·27, 2·38; 5-H: 6·44
(D)	2-Me and 6-Me: 2·55, 2·71; 5-H: 6·98
2-N_3-5-Me (B) [c]	5-Me: 2·55; 2-H and 4-H: 9·37 (d, *J* 2), 9·94br (d, *J* 2)
(E)	5-Me: 2·65; 2-H and 4-H: 9·20
2-S·NH_2-4,6-Me_2 (B)	4-Me and 6-Me: 2·39; NH_2: 3·96br; 5-H: 6·95
2-SH-4-Me (B)	4-Me: 2·30; 5-H: 6·77 (d, *J* 6); 6-H: 8·15 (d, *J* 6)
2-SH-5-Me (B)	5-Me: 2·07; 4-H and 6-H: 8·20
2-SH-4,6-Me_2 (B)	4-Me and 6-Me: 2·29; 5-H: 6·68
2-S·S-2′ (B)	5-H: 7·41 (t, *J* 5); 4-H and 6-H: 8·78 (d, *J* 5)
4,4′-Me_2-2-S·S-2′ (B)	4-Me: 2·39; 5-H: 7·25 (d, *J* 5); 6-H: 8·61 (d, *J* 5)
5,5′-Me_2-2-S·S-2′ (B)	5-Me: 2·19; 4-H and 6-H: 8·61
4,4′,6,6′-Me_4-2-S·S-2′ (B)	4-Me and 6-Me: 2·35; 5-H: 7·11
(A)	4-Me and 6-Me: 2·39; 5-H: 6·81

[a] Solvents: (A), $CDCl_3$; (B), $(CD_3)_2SO$; (C), D_2O; (D), 2M-D_2SO_4–D_2O; (E), $F_3C{\cdot}CO_2H$; pyrimidinethiones are designated mercaptopyrimidines for convenience. [b] Measured in p.p.m. at 60 MHz against Me_4Si or $Me_3Si{\cdot}[CH_2]_3{\cdot}SO_3Na$ as internal standard; singlet peaks unless indicated otherwise; *J* in Hz. [c] Present in this solvent as the tautomer, 6-methyltetrazolo-[1,5-*a*]pyrimidine (*cf.* ref. 10).

TABLE 2

U.v. spectra

Pyrimidine [a]	$\lambda_{max.}$/nm (log ε) [b]
2-SO_2F	238 (3·18), 243 (3·19), *248* (3·05)
2-SO_2F-4-Me	245 (3·33), 247 (3·33), *252* (3·22)
2-SO_2F-5-Me	243 (3·39), 248 (3·37), *256* (3·24)
2-SO_2F-4,6-Me	245 (3·38), *253* (3·25)
2-$SO_2{\cdot}NH_2$-4,6-Me_2 [c]	248 (3·52)
2-$SO_2{\cdot}NEt_2$-4,6-Me_2	247 (3·67)
2-$SO_2{\cdot}NPr^i_2$-4,6-Me_2	248 (3·45)
2-$SO_2{\cdot}N{\cdot}(CH_2{\cdot}CH_2)_2{\cdot}O$-4,6-$Me_2$	246 (3·64)
2-$SO_2{\cdot}NH{\cdot}NH_2$-4,6-Me_2	247 (4·45)
2-S·NH_2-4,6-Me_2	251 (4·04), *282* (3·51)
4,4′,6,6′-Me_4-2-S·S-2′	241 (4·30), *268* (3·93)

[a] In methanol. [b] Inflections and shoulders in italics. [c] In water.

respectively, 2-hydrazino-5-methylpyrimidine and the known 2-hydrazino-[5] or 2-diethylamino-4,6-dimethylpyrimidine[6] (3; R = $NH{\cdot}NH_2$ or NEt_2); the sulphonate groups were displaced similarly by hydrazine from the potassium salt (2; R = Me, X = OK) and its isomer, potassium 2,4-dimethylpyrimidine-6-sulphonate,[1] to give the amines (3; R = $NH{\cdot}NH_2$)[5] and (4),[7] respectively. When the concentration of free hydrazine was restricted during the preparation of the amine (4), in the unrealized hope of detecting an intermediate sulphonohydrazide, the dipyrimidin-6-ylhydrazine (5) was obtained as a by-product. The structure (5), analogous to that of a homologue described by Miller and Rose,[8] was consistent with the mass spectrum {*m/e* 244·14372 (M^+, 100%), 137·08261 [33%, ion (6) (metastable peak at *m/e* 77)], and 123·07950 [9%, ion (7)]}.

Complete displacement of the sulphonyl fluoride group also occurred on warming 5-methylpyrimidine-2-sulphonyl fluoride or its analogue (2; R = Me, X = F) with methanolic sodium azide to give, respectively, 2-azido-5-methylpyrimidine or the known[9] azide (3; R = N_3); the latter contained initially a little of the corresponding sulphonamide (2; R = Me, X = NH_2). The foregoing azidopyrimidines are in tautomeric equilibrium[10] with 6-methyl- and 5,7-dimethyl-tetrazolo[1,5-*a*]pyrimidine, respectively (see Table 1). On boiling in water the sulphonyl fluoride (2; R = Me, X = F) gave 4,6-dimethylpyrimidin-2-one; in methanolic sodium methoxide it gave the methoxypyrimidine (3; R = OMe). The rates for the latter and for three analogous reactions were measured spectrometrically: the results in Table 3

TABLE 3

Formation rates of 2-methoxypyrimidines from pyrimidine-2-sulphonyl fluorides in an excess of methanolic 0·051M-sodium methoxide at 25°

Pyrimidine	$10^3 \times k_1/s^{-1}$	$t_{\frac{1}{2}}$/s	Analyt. λ/nm
2-SO_2F	46·9	15	265
4-Me-2-SO_2F	11·7	59	265
5-Me-2-SO_2F	3·57	194	272
4,6-Me_2-2-SO_2F	3·58	193	265

suggest that a 4- or 6-methyl group decreases the reaction rate 3—4-fold, and a 5-methyl group about 12-fold. This is broadly parallel to the effect of *C*-methyl groups on the alkaline hydrolysis of potassium pyrimidine-2-sulphonates.[1]

In seeking another route to simple pyrimidinesulphonamides by oxidation of sulphenamides (*cf.* ref. 11), the thione (1; R = Me) was treated with chloramine to give the sulphenamide (3; R = $S{\cdot}NH_2$), which was separated from any remaining intermediate[12] disulphide by sublimation. The sulphenamide was unchanged on mild treatment with 3% hydrogen peroxide, *m*-chloroperoxybenzoic acid in chloroform, or potassium permanganate in acetone; treatment with 30% hydrogen peroxide in acetone or acetic acid followed by neutralization with ammonia gave a crude product clearly containing ammonium 4,6-dimethylpyrimidine-2-sulphonate (i.r. spectra[1]) but no sulphonamide was obtained. Treatment of the thione (1; R = Me) with diethylchloramine gave only bis-(4,6-dimethylpyrimidin-2-yl) disulphide, also prepared unambiguously by oxidation of the same thione with iodine or potassium permanganate in acetone; dipyrimidin-2-yl disulphide and its 4- and 5-methyl derivatives were prepared likewise for comparison. The mass spectrum of dipyrimidin-2-yl disulphide [M^+ 222 (93%)] showed an initial loss of S_2 to give a fragment of *m/e* 158 (100%), corresponding to a bipyrimidinyl; this transition was confirmed by a metastable peak at *m/e* 112·5. The subsequent breakdown pattern included not only all the peaks obtained from authentic 2,2′-bipyrimidinyl[13] but also another set: this suggested that the initial product might be a mixture of bipyrimidinyls. Bis-(4,6-dimethylpyrimidin-2-yl) disulphide behaved similarly.

In the course of this work it was found that simple potassium pyrimidinesulphonates could be prepared conveniently by the addition of aqueous potassium permanganate to appropriate pyrimidinethiones in aqueous ethanol until colouration persisted. The process was a marked improvement over treatment of a chloropyrimidine with potassium sulphite, a method[1] which gave sulphonates contaminated with potassium chloride, difficult or impossible to remove. The oxidative method was tested in typical preparations of the following: potassium 5-methylpyrimidine-2-sulphonate, the analogue (2; R = Me, X = OK), potassium 4-methylpyrimidine-6-sulphonate, and potassium pyrimidine-2(and 4)-sulphonates (both of which were unattainable by the previous method[1]).

EXPERIMENTAL

The i.r. absorptions recorded (cm^{-1}) for Nujol mulls are those associated with the $-SO_2-$ grouping;[14] they are the most intense bands in each spectrum.

Bis-(4,6-dimethylpyrimidin-2-yl) Disulphide.—4,6-Dimethylpyrimidine-2(1*H*)-thione[15] (0·25 g) in 0·2M-sodium hydroxide (10 ml) was shaken for 2 min with a solution of iodine (0·3 g) in M-potassium iodide (10 ml). The precipitate was filtered off and washed with water at 0°. The *disulphide* (96%) (from methanol) had m.p. 150—155° (according to the rate of heating) (Found: C, 51·6; H, 5·1; N, 20·1; S, 23·05. $C_{12}H_{14}N_4S_2$ requires C, 51·8; H, 5·2; N, 20·3; S, 22·7%).

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Bis-(4-methylpyrimidin-2-yl) Disulphide.—A solution of 4-methylpyrimidine-2(1*H*)-thione hydrochloride [16] (0·25 g) in water (5 ml) was adjusted to pH 7 with saturated aqueous sodium hydrogen carbonate. A 3% solution of iodine in M-potassium iodide was added dropwise with stirring until a colouration persisted for 10—15 s. Filtration gave the disulphide (73%), m.p. 104° (from methanol) (Found: N, 22·15; S, 25·8. $C_{10}H_{10}N_4S_2$ requires N, 22·4; S, 25·6%).

Bis-(5-methylpyrimidin-2-yl) Disulphide.—Treatment of 5-methylpyrimidine-2(1*H*)-thione [17] like its 4-methyl isomer gave the *disulphide* (88%), m.p. 178—179° (from ethanol) (Found: C, 47·7; H, 3·8; N, 22·6; S, 25·5. $C_{10}H_{10}N_4S_2$ requires C, 48·0; H, 4·0; N, 22·4; S, 25·6%).

Dipyrimidin-2-yl Disulphide.—Similar oxidation of pyrimidine-2(1*H*)-thione gave this *disulphide* (85%), m.p. 136° (from methanol; *cf.* ref. 18) (Found: C, 43·45; H, 2·55; N, 24·9; S, 28·65. $C_8H_6N_4S_2$ requires C, 43·2; H, 2·7; N, 25·2; S, 28·9%).

4,6-Dimethylpyrimidine-2-sulphonyl Fluoride.—A steady stream of chlorine was passed for *ca.* 30 min into a stirred mixture of 4,6-dimethylpyrimidine-2-thione [15] (7·0 g), potassium hydrogen difluoride (39 g), water (25 ml), and methanol (25 ml) maintained in a polypropylene flask at $< -10°$. The end of the reaction was confirmed by a lack of tendency for the temperature to rise and by immediate bleaching of litmus paper by a drop of the mixture. The slurry was added immediately to crushed ice (*ca.* 150 g). The solid was filtered off and washed with water at 0° until the washings were pH >3. Dried *in vacuo*, the *sulphonyl fluoride* (78%) had m.p. 58° (from diethyl ether), $\nu_{max.}$ 1195 (Found: C, 38·05; H, 3·9; S, 17·0. $C_6H_7FN_2O_2S$ requires C, 37·9; H, 3·7; S, 16·9%).

Other Sulphonyl Fluorides.—Pyrimidine-2-thione and its 4- and 5-methyl derivatives were each treated as above up to the stage of addition to crushed ice. Each suspension was then extracted with ether. The extract was washed with a little aqueous sodium hydrogen carbonate, dehydrated, and evaporated to give, respectively, *pyrimidine-2-sulphonyl fluoride* (90%), m.p. 57° (from ethanol), $\nu_{max.}$ 1158 and 1250 (Found: N, 17·0; S, 19·9. $C_4H_3FN_2O_2S$ requires N, 17·25; S, 19·8%); *4-methylpyrimidine-2-sulphonyl fluoride* (75%), b.p. 101—102° at 0·3 mmHg, $\nu_{max.}$ 1168 and 1204 (Found: C, 34·3; H, 2·6; S, 18·6. $C_5H_5FN_2O_2S$ requires C, 34·4; H, 2·85; S, 18·2%); and *5-methylpyrimidine-2-sulphonyl fluoride* (>95%), m.p. 76—77° (from ethanol), $\nu_{max.}$ 1145 and 1220 (Found: C, 34·5; H, 2·9; S, 18·5%).

4,6-Dimethylpyrimidine-2-sulphonamide.—(*a*) 4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0·5 g) was added to liquid ammonia (*ca.* 5 ml). After 5 min, the mixture was filtered and allowed to evaporate. The residual sulphonamide (82%) had m.p. 198—199° (from aqueous methanol) (lit.,[2] 200°), $\nu_{max.}$ 1158 (Found: N, 22·5. Calc. for $C_6H_9N_3O_2S$: N, 22·45%).

(*b*) 4,6-Dimethylpyrimidine-2-thione [15] (1·4 g) in M-potassium hydroxide (10 ml) was maintained at *ca.* −10° while a stream of chlorine was passed in for 35 min. The solid was filtered off immediately, washed with cold water, and added in portions to liquid ammonia (*ca.* 10 ml). A small amount of undissolved disulphide (identified by mixed m.p.) was filtered off. The residue from evaporation was recrystallized from water to give the same sulphonamide (44%) as in (*a*).

Other Sulphonamides.—Using method (*a*), pyrimidine-2-sulphonyl fluoride and its 4- and 5-methyl derivatives were converted respectively into pyrimidine-2-sulphonamide, m.p. 181° (lit.,[2] 181°); *4-methylpyrimidine-2-sulphonamide* (79%), m.p. 163° (from aqueous ethanol) (Found: C, 35·05; H, 4·1; N, 24·0; S, 18·2. $C_5H_7N_3O_2S$ requires C, 35·0; H, 4·1; N, 24·3; S, 18·5%) [from some batches, another crystalline form (which melted at 151°, resolidified, and remelted at 163°) was isolated (Found: N, 24·3; S, 18·6%)]; and *5-methylpyrimidine-2-sulphonamide*, m.p. 151—152°, $\nu_{max.}$ 1120 and 1185 (Found: C, 34·9; H, 4·2; N, 24·0; S, 18·6%).

4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0·5 g) was added to ethanolic 30% ethylamine (5 ml). After 5 min, the solution was evaporated. The residue was triturated with a little cold water and recrystallized from aqueous ethanol to give N(2)-*ethyl*-4,6-*dimethylpyrimidine*-2-*sulphonamide* (*ca.* 10%), m.p. 130—131° (Found: C, 44·9; H, 6·3; S, 14·9. $C_8H_{13}N_3O_2S$ requires C, 44·5; H, 6·1; S, 14·9%). The same substrate (0·5 g) and neat diethylamine (5 ml) were boiled under reflux for 5 min. Filtration and evaporation gave N(2)N(2)-*diethyl*-4,6-*dimethylpyrimidine*-2-*sulphonamide* (>90%), m.p. 60° (from aqueous ethanol), $\nu_{max.}$ 1145, 1170, and 1195 (Found: C, 49·5; H, 7·4; N, 17·3; S, 13·3. $C_{10}H_{17}N_3O_2S$ requires C, 49·4; H, 7·0; N, 17·3; S, 13·2%). Similar treatment of the fluoride with morpholine (100° for ½ h) or di-isopropylamine (80° for 4 h) gave respectively 4,6-*dimethylpyrimidine*-2-*sulphonomorpholide* (93%), m.p. 159—160° (from diethyl ether), $\nu_{max.}$ 1110 and 1150 (Found: C, 46·6; H, 6·0; N, 16·3; S, 12·5. $C_{10}H_{15}N_3O_3S$ requires C, 46·7; H, 5·9; N, 16·3; S, 12·5%); and N(2)N(2)-*di-isopropyl*-4,6-*dimethylpyrimidine*-2-*sulphonamide* [40% directly and a further 44% by elution of the mother liquor contents from a silica column first with chloroform (rejected) and then with ethanol (retained)], m.p. 235° (decomp.) (from aqueous ethanol), $\nu_{max.}$ 1160, 1185, and 1230 [Found (for material dried at 25°): C, 49·6; H, 8·3; N, 14·45. $C_{12}H_{21}N_3O_2S,H_2O$ requires C, 49·8; H, 8·0; N, 14·5%].

4,6-Dimethylpyrimidine-2-sulphonohydrazide.—Hydrazine hydrate (0·5 ml) in methanol (1 ml) was added in drops to an agitated solution of 4,6-dimethylpyrimidine-2-sulphonyl fluoride (1·0 g) in methanol (5 ml) maintained at −10 to −15°. The mixture was filtered at once. [The filtrate contained 2-hydrazino-4,6-dimethylpyrimidine which increased in amount if the reaction was prolonged.] The solid, dissolved in chloroform, was washed with a little water. The chloroform layer was dried and evaporated to give the *sulphonohydrazide* (40%), m.p. 124—125° (from ethanol), $\nu_{max.}$ 1160 (Found: C, 35·7; H, 5·2; S, 15·8. $C_6H_{10}N_4O_2S$ requires C, 35·6; H, 5·0; S, 15·9%). This material (0·05 g) was boiled under reflux in acetone (2 ml) for 5 min. Filtration and evaporation gave a solid, which was dissolved in chloroform, washed with water, and recovered by evaporation. Recrystallized from ethanol, N(2)-*isopropylidene*-4,6-*dimethylpyrimidine*-2-*sulphonohydrazide* (92%) had m.p. 171°, $\nu_{max.}$ 1160 (Found: C, 44·8; H, 6·25; N, 22·75; S, 13·2. $C_9H_{14}N_4O_2S$ requires C, 44·6; H, 5·85; N, 23·1; S, 13·25%).

2-*Hydrazino*-4,6-*dimethylpyrimidine.*—(*a*) A mixture of

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4,6-dimethylpyrimidine-2-sulphonohydrazide, -sulphonamide, or -sulphonyl fluoride (0·5 g) with hydrazine hydrate (2 ml) in methanol (10 ml) was boiled under reflux for 1 h. The residue from evaporation was mixed with water (25 ml) and extracted with chloroform (4 × 15 ml). Evaporation of the extract and sublimation (100° at 0·2 mmHg) gave the 2-hydrazino-dimethylpyrimidine (>95%), m.p. 162° (lit.,[5] 165°) (Found: C, 52·3; H, 7·65; N, 40·5. Calc. for $C_6H_{10}N_4$: C, 52·2; H, 7·25; N, 40·6%).

(*b*) Potassium 4,6-dimethylpyrimidine-2-sulphonate [1] was treated with hydrazine as in (*a*) but with 50% aqueous ethanol as solvent. The sublimed product (41%) was identified with that in (*a*) by mixed m.p.

4-Hydrazino-2,6-dimethylpyrimidine.—(*a*) Potassium 2,4-dimethylpyrimidine-6-sulphonate [1] underwent hydrazinolysis like its isomer to give the 4-hydrazinodimethylpyrimidine (56%), m.p. 186—187° (lit.,[7] 186—187°) (Found: C, 52·5; H, 7·5; N, 40·05. Calc. for $C_6H_{10}N_4$: C, 52·5; H, 7·25; N, 40·6%).

(*b*) A solution of the same sulphonate (0·5 g) and hydrazine sulphate (0·5 g) in 50% aqueous ethanol (10 ml) was adjusted to pH 7 by addition of hydrazine hydrate. After boiling under reflux for 45 min, water (25 ml) was added, and the mixture was extracted with chloroform. Evaporation of the extract and sublimation gave the same product (41%) as in (*a*). The unsublimed residue crystallized from ethanol to give a little *NN'-bis-2,4-dimethylpyrimidin-6-ylhydrazine*, m.p. 255—256°, M^+, 244·14372 ($C_{12}H_{16}N_6$ requires *M*, 244·14364), $\lambda_{max.}$ (MeOH) 235 (log ε 4·23) and 272 nm (4·08) [*cf.* 2-propyl-homologue,[8] 228 (4·15) and 273 (4·05)].

2-Diethylamino-4,6-dimethylpyrimidine.— 4,6-Dimethylpyrimidine-2-sulphonyl fluoride (1·0 g) and diethylamine (10 ml) were heated in a sealed tube at 150° for 4 h. Evaporation and sublimation (25° at 0·2 mmHg) of the residue gave the diethylaminodimethylpyrimidine (60%), identified with authentic material [6] by mixed m.p., t.l.c., and i.r. spectra.

2-Hydrazino-5-methylpyrimidine.—Hydrazine hydrate (2·5 ml) was added to 5-methylpyrimidine-2-sulphonyl fluoride (0·18 g) in methanol (2·5 ml). After the vigorous reaction, the mixture was boiled under reflux for 30 min. The residue from partial evaporation was added to water (10 ml) and the solution was adjusted to pH 8 with hydrochloric acid. Extraction with chloroform, evaporation of the extract, and sublimation (80° at 0·1 mmHg) gave the *hydrazinomethylpyrimidine* (>90%), m.p. 143—144° (Found: C, 48·5; H, 6·5; N, 45·2. $C_5H_8N_4$ requires C, 48·4; H, 6·5; N, 45·1%).

2-Azido-5-methylpyrimidine.— 5-Methylpyrimidine-2-sulphonyl fluoride (0·18 g) in methanol (0·5 ml) was added to sodium azide (0·07 g) in water (0·3 ml). After 24 h the mixture was evaporated to dryness and extracted with anhydrous methanol. Evaporation to small bulk followed by preparative t.l.c. on silica (chloroform–5% methanol) separated two compounds: the *azidomethylpyrimidine* (55%), m.p. 123° (Found: C, 44·0; H, 3·8; N, 51·85. $C_5H_5N_5$ requires C, 44·4; H, 3·7; N, 51·8%), and a minor unidentified product.

2-Azido-4,6-dimethylpyrimidine.— 4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0·19 g) in methanol (0·5 g) was stirred at 50° for 1 h with sodium azide (0·07 g) in water (0·3 ml). After 24 h, the residue from evaporating the mixture was extracted with anhydrous methanol, and the extract was again reduced to dryness. Recrystallization (with concentration) from ethanol–water (1 : 2) gave the bulk of the product; submission of the residual solution to preparative t.l.c. (silica; chloroform–5% methanol) separated a little more product from a by-product. The azidopyrimidine (69%), had the same m.p. (154—155°) and i.r. spectrum as authentic material; [9,10] the by-product (14%) was shown to be 4,6-dimethylpyrimidine-2-sulphonamide by mixed m.p. and i.r. spectra.

4,6-Dimethylpyrimidin-2(1H)-one.— 4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0·25 g) and water (2·5 ml) were boiled under reflux until the mixture was homogeneous (*ca.* 45 min). The solution was adjusted to pH 2 with sodium hydroxide and evaporated to dryness, using azeotropic distillation with chloroform to remove the last traces of water. The solid was extracted in a Soxhlet apparatus by ethyl acetate. Evaporation of the extract and recrystallization from ethanol gave the pyrimidinone (47%), identified with authentic material [19] by mixed m.p. (199°) and i.r. spectra.

2-Methoxy-4,6-dimethylpyrimidine.— 4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0·5 g) and methanolic sodium methoxide [from sodium (0·1 g) and methanol (25 ml)] were boiled under reflux for 1·5 h. The residue from removal of solvent was diluted with water (10 ml) and extracted with chloroform (5 × 15 ml). The oil obtained on evaporation of the extract was triturated with aqueous sodium hydrogen carbonate and re-extracted into ether. Evaporation gave the methoxypyrimidine (60%), identified with authentic material [20] by i.r. spectra and as its picrate, m.p. 137—138° (lit.,[21] 137—138°). The sulphonyl fluoride was recovered unchanged after being boiled with anhydrous methanol under reflux for 5 h.

Rate Measurements.—Rates for the reactions of four pyrimidine-2-sulphonyl fluorides with methanolic sodium methoxide were measured as follows. Equal volumes of a methanolic 2—3 × 10^{-4}M-solution of the sulphonyl fluoride and of methanolic 0·103M-sodium methoxide were mixed in an all-polytetrafluoroethylene stopped-flow rapid-reaction apparatus [22] thermostatted at 25 ± 0·1° and attached to a Shimadzu RS27 spectrophotometer recording optical density (at a predetermined wavelength: Table 3) against time. Rates for these pseudo-first-order reactions were calculated from the general equation, $k = 1/t \times \ln[a/(a - x)]$, and expressed as first order constants (s^{-1}) under the defined conditions. Each reaction was followed at least from 15 to 75% completion, in which range the standard deviation was <3%. The whole u.v. spectrum of each solution, recorded after *ca.* 5 × $t_{\frac{1}{2}}$, closely resembled that of the expected product: 2-methoxypyrimidine [23] or its 4-methyl-,[24] 5-methyl-,[25] or 4,6-dimethyl-derivative.[26]

4,6-Dimethylpyrimidine-2-sulphenamide.— Commercial 1·4M-sodium hypochlorite solution (15 ml) was cooled to <0° and added to similarly cooled 1·4M-ammonia (40 ml). The resulting solution of chloramine was mixed with a solution of 4,6-dimethylpyrimidine-2-thione [15] (1·4 g) in

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[25] D. J. Brown and T.-C. Lee, *Austral. J. Chem.*, 1968, **21**, 243.
[26] M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 1952, 3722.

2M-potassium hydroxide (5 ml), also at <0°. The mixture was stirred until it had warmed to room temperature (*ca.* 15 min). The crystalline solid was filtered off and washed with a little ice-cold water. Dried at 25° *in vacuo*, the *sulphemamide* (25%) had m.p. 99—100° [after sublimation (90° and 1 mmHg)] (Found: C, 46·4; H, 6·15; N, 27·0; S, 20·95. $C_6H_9N_3S$ requires C, 46·45; H, 5·85; N, 27·1; S, 20·65%). When 5M-ammonia was substituted for potassium hydroxide the crude product gave the sulphenamide (11%) by sublimation; the residue was bis-(4,6-dimethylpyrimidin-2-yl) disulphide (59%), identified by i.r. spectra and mixed m.p. with authentic material.

Potassium Pyrimidinesulphonates.—The oxidation of pyrimidinethiones is a better method to make potassium pyrimidinesulphonates free of inorganic salts than is the recently described [1] treatment of chloropyrimidines with potassium sulphite.

Aqueous 0·05M-potassium permanganate was added in drops to a shaken slurry of 4,6-dimethylpyrimidine-2-thione [15] (0·7 g) in 50% aqueous ethanol (20 ml) until a pink colour persisted for 10—15 s. After 10 min the manganese dioxide was filtered off and washed with aqueous ethanol. The combined filtrate and washings were evaporated and the last traces of water were removed by co-distillation with chloroform. The residue, which was completely soluble in boiling anhydrous methanol, was recrystallized from aqueous ethanol to give potassium 4,6-dimethylpyrimidine-2-sulphonate (65%), m.p. 295° (decomp.), identified with authentic material [1] by i.r. spectra and m.p. (Found: C, 31·65; H, 3·1; K, 17·4; S, 13·9. Calc. for $C_6H_7KN_2O_3S$: C, 31·8; H, 3·1; K, 17·3; S, 14·1%).

Similar oxidation of 5-methylpyrimidine-2-thione [17] (0·63 g) gave a crude product containing some disulphide. This was removed by dissolution of the sulphonate in water (12 ml)) and filtering. Evaporation of the aqueous filtrate and recrystallization gave *potassium 5-methylpyrimidine-2-sulphonate* (76%), decomposing above 310° and identical in i.r. spectra with the salt-containing specimen previously described [1] (Found: C, 28·1; H, 2·2; S, 15·1. $C_5H_5KN_2O_3S$ requires C, 28·3; H, 2·4; S, 15·1%).

In a similar way, 4-methylpyrimidine-6-thione [24] gave *potassium 4-methylpyrimidine-6-sulphonate* (>90%), m.p. 259—260° (Found: K, 18·6; S, 14·8. $C_5H_5KN_2O_3S$ requires K, 18·4; S, 15·1%); pyrimidine-2-thione gave [oxidized at *ca.* 5°; disulphide removed from crude product by extraction with chloroform] *potassium pyrimidine-2-sulphonate* (74%), m.p. 328° (decomp.), $\nu_{max.}$ 1032, 1205, and 1250 (*cf.* ref. 1), and $\lambda_{max.}$ (H_2O) 243·5sh (log ε 3·30) and 246 nm (3·33) (*cf.* ref. 1) (Found: C, 23·9; H, 1·4; K, 19·9; N, 13·8; S, 15·9. $C_4H_3KN_2O_3S$ requires C, 24·2; H, 1·5; K, 19·7; N, 14·1; S, 16·2%); pyrimidine-4-thione [27] gave [like its isomer; oxidized at *ca.* 5°] *potassium pyrimidine-4-sulphonate* (>90%), m.p. 330° (decomp.), $\nu_{max.}$ 1044, 1215, and 1230, pK'_a −0·53 ± 0·02 (analyt. λ 255 nm) (*cf.* predicted [1] value −0·4), $\lambda_{max.}$ (H_2O) 245·5sh (log ε 3·60), 250·5 (3·65), and 256sh nm (3·51), δ (D_2O) 8·11 (q $J_{5,6}$ 5, $J_{2,5}$ 1·3 Hz, 5-H), 9·18 (d, $J_{5,6}$ 5 Hz, 6-H), and 9·41br p.p.m. (2-H) (Found: C, 24·5; H, 1·6; K, 19·5; N, 14·1; S, 15·9%). The rate of alkaline hydrolysis of potassium pyrimidine-4-sulphonate as a *ca.* 1×10^{-4}M-soln. in N-NaOH was determined spectrophotometrically at 232 nm (see ref. 1 for details).

T/°C	$k \times 10^{-5}$/s^{-1} [a]	$t_{\frac{1}{2}}$/min
40	275 (*ca.* 100)	4·2
25	77·9 (91)	14·8

[a] Reaction followed from <10% to % in parentheses.

We thank Dr D. D. Bly (E. I. du Pont de Nemours, Wilmington) for a gift of 2,2′-bipyrimidinyl, Drs G. B. Barlin and T. J. Batterham for discussions, Dr J. E. Fildes and her staff for analyses, Dr J. K. MacLeod for mass spectra, Mr S. E. Brown for ^{1}H n.m.r. spectra, and the Australian National University for supporting J. A. H. as a Research Scholar.

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[27] W. L. F. Armarego, *J. Chem. Soc.*, 1965, 2778.

ERRATA

STUDIES ON PYRIMIDINESULPHONIC ACIDS AND RELATED COMPOUNDS: SYNTHESES AND METATHESES

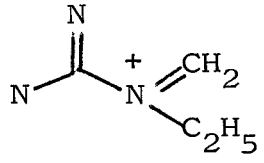
By J. A. Hoskins

P. 75 Lines 3 and 4 should read:- "Either the molecular ion lost diimide or there was rupture of the N-N bond to give a "

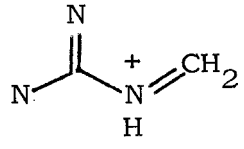
P. 76 Delete from line 1 the word "empirical"

P. 77 Lines 5 and 6 should read:- "4-Hydrazinoquinazoline first lost a diimide molecule to give a quinazoline ion which then"

P. 78 Replace the formula of m/e 186 by:-



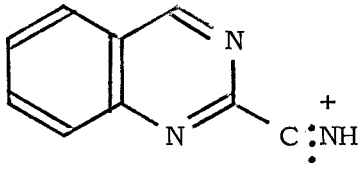
Replace the formula of m/e 158 by:-



P. 79 Replace the formula of m/e 245 by:- $C_{12}H_{13}N_4S^+$

Replace "Bis(4,6-dimethylpyrimidinyl)$^+$ " by:- $C_{12}H_{13}N_4^+$

P. 81 Replace formula of m/e 156 by:-



24th July, 1972